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ANNALS OF
INTERNAL MEDICINE

VOLUME 7 FEBRUARY, 1934 NUMBER 8

RATIONAL TREATMENT OF THE ANEMIC PATIENT *

By WILLIAM P. MURPHY, M.D., *Boston, Massachusetts*

ADEQUATE treatment for anemia is that which produces and maintains the best state of health possible for the individual patient. The best treatment is that which is adequate and is available at a minimum of inconvenience and expense. Rational treatment is the best treatment expedient for the patient whose particular problem is under consideration.

The treatment which may be considered rational for improving the condition of the blood may not be so for its maintenance in a satisfactory condition, or for maintenance of the patient in a proper state of health thereafter. An example of this situation is the following: A patient recently came to my office with the desire to know whether or not liver and iron, which had been advised, must be continued indefinitely. Anemia had been found but the kind not determined. There had been transient soreness of the tongue and numbness of the hands: the level of the hemoglobin and of the red blood cell count were normal at my office. The blood appeared normal in a stained smear, and the size of the cells was found to be normal. In other words, there were no characteristic findings in the history, physical examination or blood from which a diagnosis could be made. Should such a patient continue taking large amounts of liver for life or run the risk of the serious consequences which might follow omission of it?

The lesson to be learned from this patient's experience is that rational treatment is possible only after a correct diagnosis is made. This may be possible in some instances only during the time that anemia is present.

The importance of careful routine examinations of the blood cannot be minimized in spite of the fact that one may expect, by administering large doses of liver and of iron, to produce improvement of the blood in practically all forms of anemia that will respond to treatment. Nearly all patients are within reach of a laboratory so equipped that the simple hematological studies necessary to make a diagnosis are available. A simple, though accurate, determination of the hemoglobin value and examination of a stained smear of the blood are often sufficient to suggest the diagnosis

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

which may be confirmed by a count of the red and white blood cells and a determination of the individual cell volume.

An examination of the blood may not in itself be sufficient to establish a diagnosis, particularly if little change has occurred therein. Usually, however, a careful analysis of the history and physical findings together with the results of the blood tests will make a diagnosis possible. In table 1 are shown the more important points to be considered in determining the

TABLE I

PERNICIOUS ANEMIA

Signs and Symptoms

Weakness

Pallor (lemon yellow)

Gastrointestinal	Neuro-muscular
Sore tongue or mouth, persistent	Numbness and tingling, persistent
Diarrhea, intermittent	Cold and tightness
Nausea and vomiting	Disturbed locomotion

Blood

Anemia
- Macrocytosis (increased cell volume and diameter)
- Poikilocytosis (tailed forms)
- Hyperchromia (high color and iron index)
- Leukopenia (old or multilobulated polymorphonuclear leukocytes)

Hyperbilirubinemia (increased icteric index)

diagnosis of pernicious anemia. If after a careful review of the above mentioned features, there is still doubt as to the diagnosis, important evidence may be obtained by a therapeutic test. By this I mean observation of the reticulocytes during a period of 10 to 14 days following the institution of liver therapy. The prompt and striking increase in these cells during the 10 days immediately following the beginning of liver treatment is practically limited to patients with pernicious anemia whose blood is in a state of relapse. It is of practical importance for this reason to arrange to follow the reticulocyte curve.

Differentiation of the secondary anemias, now more logically designated as hypochromic, from pernicious anemia is generally possible by means of the blood examination. The presence of anemia may be anticipated by pallor of the mucous membranes or even of the skin in some instances. It is difficult to indicate any constant or characteristic symptoms of this group, although weakness, ease of fatiguability, and aggravation of symptoms not strictly the result of the anemia often occur even with apparent slight degrees of anemia. Because of the striking improvement which generally results from adequate treatment, even in the mild anemic states, it is rational to make an effort to eliminate the anemia in all patients. Anemia will often be a cause for increased disability in such conditions as myocardial weakness, angina pectoris, peptic ulcer, myxedema, syphilis, etc., in which conditions the most complete improvement possible may be brought about only with treatment of the anemia as well as of the fundamental disease condition.

Pernicious Anemia

Assuming that a diagnosis of pernicious anemia has been made, the next step is to institute promptly and carry out intensively a rational regimen of treatment with liver. Failure to treat a patient so diagnosed is inexcusable and can lead only to the most unfortunate consequences. Carelessness or a casual approach in instituting or carrying on the regimen can not produce the best results. Some years ago when only liver was available for use and little was known generally in regard to treatment, a patient was seen in consultation at some distance and advised to take one-half pound of liver per day. The regimen was necessary but difficult for this patient to carry out. A few days later I received a telegram from the patient's physician saying that the nurse did not believe that the treatment would be effective and would not encourage its use. What should be done? My reply was, " Fire the nurse and get a new one." The patient's blood has remained in satisfactory condition for over six years.

Only with the most meticulous attention to the details of the patient's needs and intelligent encouragement at regular intervals may one hope to get the results which are possible with the liver treatment. For the patient who has no difficulty in consuming adequate amounts of whole liver, either raw or cooked, one need hardly encourage the use of any substitute for it. There are, however, patients who find difficulty in doing this. Fortunately for such individuals, there are now substitutes for liver which may be used with entire satisfaction. These substitutes are available for peroral or for parenteral use.

Many liver preparations to be taken perorally are now marketed for use in treating pernicious anemia. They are not all of equal potency, however, and some are even of distinctly little value. Unfortunately there are also on the market a number of preparations containing liver which are sold for general use in " anemia," which lack even a trace of value for the pernicious anemia patient. In spite of the physician's watchful care the patient may be influenced by a desire to obtain a short cut to health, or may be induced by the glowing accounts of the manufacturer or dispenser of the non-potent liver-containing preparation to believe that it is possible to get well with less expense. A druggist recently persuaded one of my patients to take a preparation containing liver which he said was " less expensive and just as good " as the liver extract which she was using. The patient came to me for her customary check-up with less than 3,000,000 red cells per cubic millimeter and with evidence of beginning sclerosis of the spinal cord. There are no such short cuts to health in this disease. Only those substitutes for whole liver which contain demonstrated potency for pernicious anemia can safely be prescribed, and those with the highest degree of potency are to be recommended as the more rational form of treatment.

The introduction of substitutes for liver which may be given parenterally has made available a means of readily supplying the maximum amount of

potent material. By using large doses of the concentrated solution of liver extract intramuscularly, as I have previously described,[1, 2] optimal responses of the erythrocytes may be produced. When given in amounts of 12 c.c. (prepared from 400 gm. of liver) during the first 12 to 24 hours the erythrocytes have shown an average increase of 110,000 per day during the first week after starting treatment and during a period of 28 days 100,000 per day in patients having an initial red blood cell level of 2,000,000 or less. Increases as rapid as 140,000 to 200,000 per day have been noted during the first week and rates of increase as high as 120,000 to 135,000 per day during 28 days are not infrequent in such a group of patients.

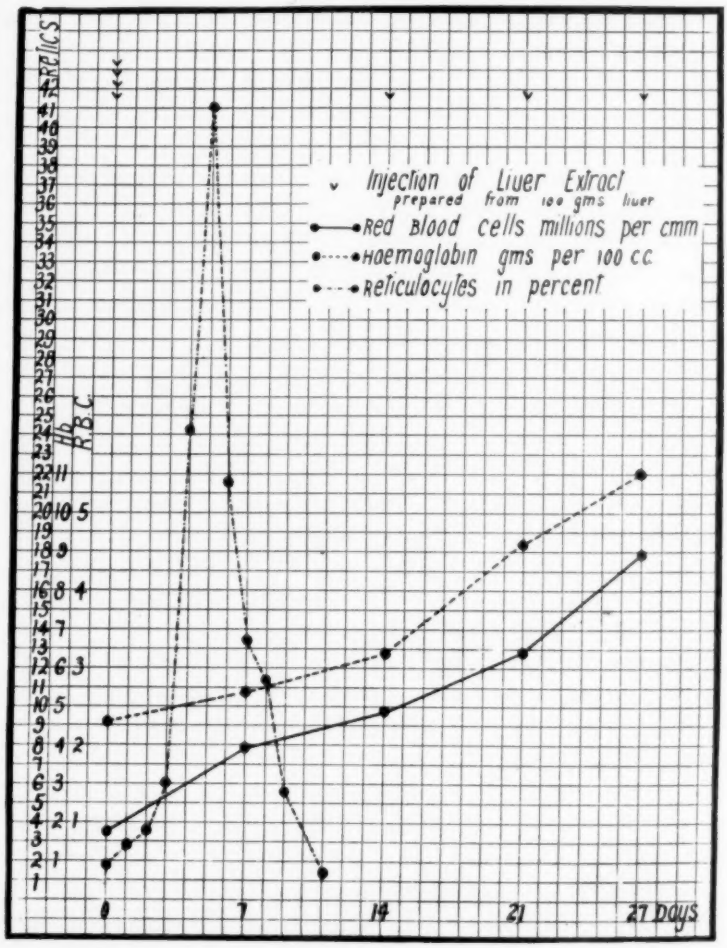

FIG. 1. The intervals at which intramuscular injections of a concentrated solution of liver extract were given to this patient are shown, together with the resulting reticulocyte and erythrocyte response.

Treatment has been carried out in various ways following the initial injection of the large amount of potent material. In some patients sub-

sequent injections of 3 c.c. (prepared from 100 gm. of liver) of the concentrated solution have been given at intervals of a week until the blood count has become normal (5,000,000 or more cells). (See figure 1.) In other patients no more has been injected for from three to five weeks during which time a maximum rate of increase of the erythrocytes occurs. (See figure 2.) The rate of increase of the erythrocytes has been essen-

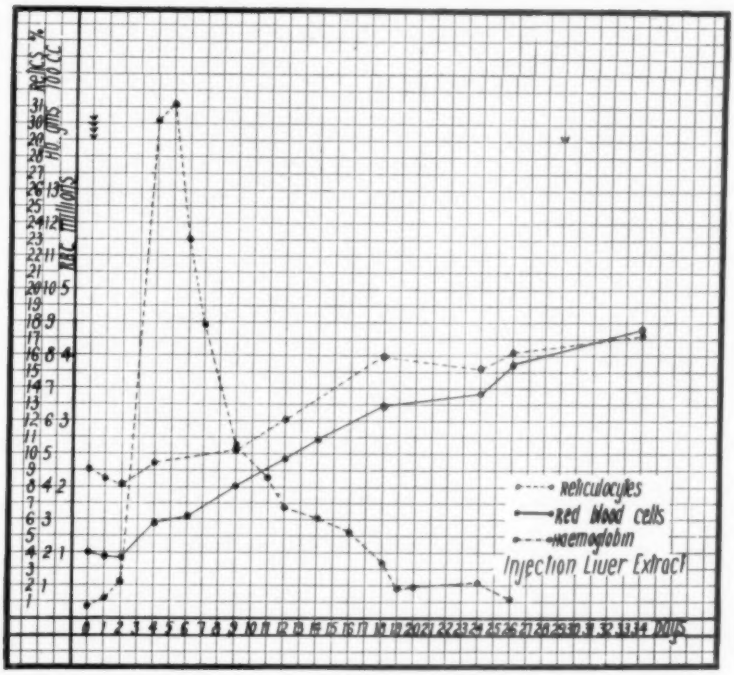

FIG. 2. Each arrow-head (v) figured in the upper portion of this chart indicates the time of injection of 3 c.c. of a concentrated solution of liver extract. The resulting reticulocyte and erythrocyte responses are shown.

tially the same with either of these methods of treatment, although the subsequent effect on erythrocyte formation of the former method seems to be greater. These observations suggest that when the potent substance is given in excess of immediate needs it is possible for the blood-forming organs to use limited amounts, and for the remainder to be stored in the body for later utilization as needed.

That it is possible for the excess of potent material to be stored is of the greatest importance in the maintenance treatment of the patient. It has recently been said [8] that it is necessary, in order to obtain the best results in maintenance with parenteral extract, for the patient to receive the material at frequent intervals (an injection preferably every day, or not less than every two to four days). That this is not necessary and that it is possible to obtain optimal results with the use of relatively infrequent injections, provided the material is highly potent and the amount used is

sufficient, is illustrated by the results obtained in our clinic with the concentrated solution of liver extract during a period of two years. A summary of the results of the maintenance treatment in 68 patients is shown in table 2. Although a number of patients have remained in excellent health

TABLE II

MAINTENANCE TREATMENT OF PATIENTS BY MEANS OF INTRAMUSCULAR INJECTIONS OF LIVER EXTRACT

Number of Patients	Interval between Injections	Range of Final Red Blood Cell Count *	Average Red Blood Cell Count
15	6 wks.	4.85–6.14	5.27
8	5 wks.	4.50–6.54	5.06
20	4 wks.	4.51–5.79	5.12
7	3 wks.	4.38–5.95	5.28
13	2 wks.	4.53–5.99	5.58
5	1 wk.	4.62–5.34	5.01

* Millions per cu. mm.
Material derived from 100 gm. of liver (3 c.c.) given at the intervals recorded.

with injections of 3 c.c. (obtained from 100 gm. of liver) at intervals greater than four weeks, it would seem wiser to give injections at intervals of four weeks or less depending upon the need of the patient. Rarely will it be necessary more often than one in one or two weeks. The patients treated as shown in table 2 have maintained a higher level of the blood and have remained in better health generally than have a similar group in our clinic under peroral treatment during a comparable period of time.

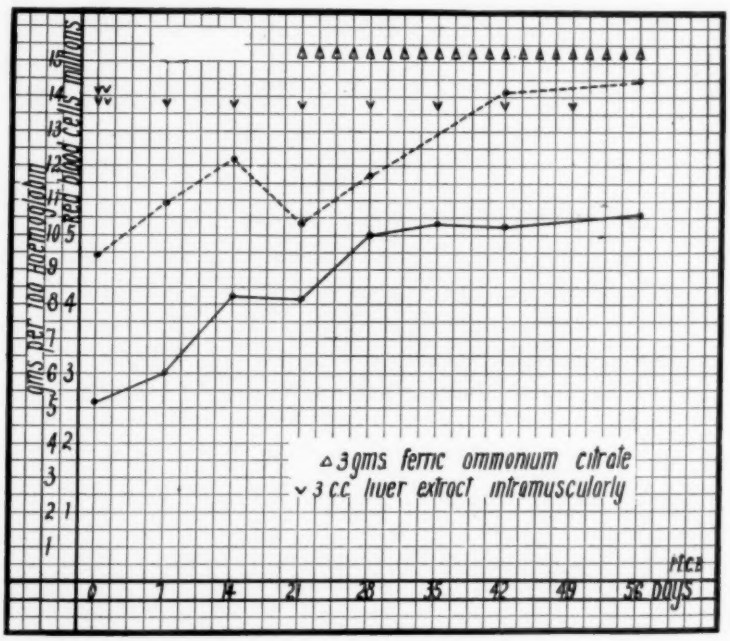

FIG. 3. The effect produced by the addition of daily, large doses of iron to the treatment of a patient with pernicious anemia by means of intramuscular injections of liver extract.

It is generally well to advise the patient to include plenty of fruit, vegetables and meat in the diet, which may be prescribed in other respects as the physician may consider advisable.[4]

Iron, in large doses, is often of value especially for those patients taking liver extract either perorally or parenterally. (See figure 3.)

The institution of exercises designed to retrain the paralyzed muscles and to improve the sense of balance of the patient is to be strongly advised for those patients with disturbed locomotion resulting from peripheral or spinal nerve sclerosis.

Secondary (Hypochromic) Anemia

The impetus given to the study of diseases of the blood during the last decade has resulted in a somewhat better understanding of some fundamental concepts of the blood diseases but has produced confusion rather than clarification of the principles underlying the treatment of the secondary or truly hypochromic anemias.

As early as 1832 Blaud demonstrated the value of large doses of iron in the treatment of chlorosis. This treatment is still as effective in the anemias with iron deficiency as it was in the days of Blaud. Studies carried out in the author's laboratory of the Peter Bent Brigham Hospital[6] over a period of several years have helped to establish several facts in regard to the treatment of anemia with iron deficiency upon the basis of which rational treatment for this form of anemia may be prescribed. (See figure 4.)

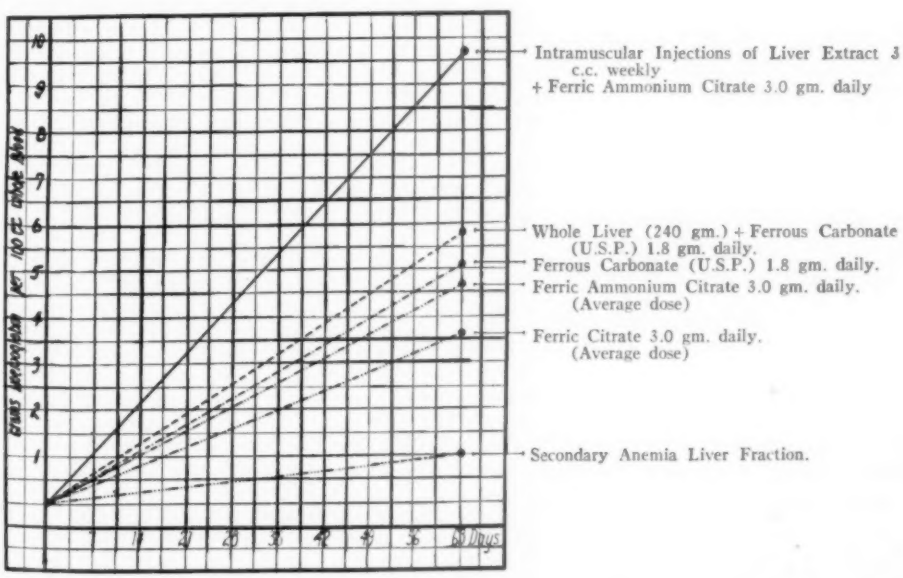

Fig. 4. Diagram indicating the average increase in hemoglobin produced by various methods of treatment throughout a period of 63 days.

The effectiveness of large doses of iron, administered in the form of ferrous carbonate (U.S.P.) or as ferric ammonium citrate (U.S.P.) in solution or capsule, has been confirmed, whereas iron therapy with ferric citrate appears to be somewhat less effective. It has been found that whole liver administered in large amounts may be substituted for iron but is not superior to it and is more difficult to take. When liver is given together with iron the effect is greater than is that of either given alone. Liver extracts, either fraction G of Cohn or the secondary anemia fraction of Whipple when taken perorally, have not been effective in materially increasing the hemoglobin of anemic patients. Solution of liver extract administered intramuscularly has no apparent effect on the formation of hemoglobin if given alone, but when it is given in combination with large doses of iron perorally there results a more rapid response of the hemoglobin and red blood cells than occurs with the use of a similar amount of iron alone. The preparations containing iron and copper have shown no effects greater than those which might be expected from the iron contained therein.

In consideration of these facts it should not be difficult to advise a rational regimen of treatment for the patient with secondary or hypochromic anemia. Ferrous carbonate (U.S.P.) in daily amounts (4 gm.) sufficient to supply about 400 mg. of iron, and ferric ammonium citrate (U.S.P.) in amounts (3 gm.) to supply 500 mg. have produced satisfactory clinical results. Evidence available now indicates that larger doses of iron are not more effective and therefore are generally unnecessary. For hastening the improvement of the blood, and especially the patient's general physical condition, an intramuscular injection of 3 c.c. (prepared from 100 gm. of liver) of concentrated liver extract (Lederle) at intervals of five to seven days, together with the peroral use of iron, is to be advised. Regulation of the diet may be important in some instances where the dietary habits have been bad. Whole liver may, under some circumstances, be recommended in addition to the iron as the combined effect is greater than that of either alone.

Rational treatment can hardly include combinations of liver extract, ventriculin, copper, vitamins, etc., together with iron, as there is not as yet evidence to indicate that such combinations are more effective in the anemia of man than the iron contained therein, and they are often less palatable and invariably many times more expensive.

Discussion

The basic principles of the rational treatment of anemia, viewed in the light of our present knowledge, appear to be simple and clear cut. It is not only the physician's duty and desire to prescribe for his patient that form of treatment which will most quickly and certainly restore him to a state of good health and economic efficiency, but also to accomplish this with a minimum of expense to him.

The Committee on the Cost of Medical Care [6] has found that 18 per cent

of the cost of medical care is for medicine. There are available in this country alone for the treatment of anemia at least 16 special preparations other than the simple iron salts and the substitutes for liver which are sold specifically for use in pernicious anemia. Of the latter there are at least 18 preparations available. Recognition of the importance of the iron deficiency which occurs in the patient with secondary or hypochromic anemia and of the value of certain of the simple iron salts in relieving this deficiency will help to reduce the 18 per cent cost of medicine.

Clear and frank presentations of the clinical results of the treatment of patients with similar disease conditions, with sufficient data recorded so that such results may be readily compared with those in other published studies, are to be encouraged. Complicated interpretations of data with figures difficult to analyze can lead only to confusion. Brief descriptions of the methods employed in treatment and for recording data are usually of value. The use in the laboratory of instruments of recognized precision and standardization for recording the results is indispensable.

Commendable progress toward the recognition of those preparations which have demonstrated value in the treatment of the condition for which they are advocated has been made by the Council on Pharmacy and Chemistry of the American Medical Association; and the newer arrangement of New and Non-Official Remedies should make this information more generally available. The publication each year, by some similarly unbiased committee, of a brief, critical review of those preparations which have demonstrated value and of those methods of treatment which have reasonable assurance of practical success as determined by reports during the current year is suggested. Such a review might be published in the form of a pamphlet at small cost and made easily available to all physicians.

Further progress will be possible in the direction of the rationalization of treatment and away from exploitation of the patient when a sharper distinction is made between the reports of research studies which are of experimental or purely scientific interest and those which are of a more practical or clinical nature, and when the latter type of research receives the recognition by the medical profession which is commensurate with its importance in the maintenance of the health of the patient. The medical man can make no greater contribution than this to society.

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THE USE OF GLYCINE IN THE TREATMENT OF MYASTHENIA GRAVIS *

By Earl O. G. Schmitt, M.D., F.A.C.P., *San Jose, California*

Definition

Myasthenia gravis, or Erb-Goldflam disease, may be defined as a disease characterized by an incapacity on the part of the voluntary motor system for sustained effort.[1] It is a disease of the muscles themselves without involvement of the nervous system and affects most commonly the muscles of the eyes, those of the face, and the muscles of mastication.

Historical

The disease was first described by Wilkes in 1877. Erb, in 1878, characterized the condition as being a combination of bulbar symptoms, ptosis, and weakness of the muscles of mastication and of the muscles of the back of the neck. In 1887 Oppenheim published a report of "a case of chronic progressive bulbar paralysis without anatomic findings," emphasizing the absence of muscular atrophy, the absence of disturbances of electrical excitability in the muscles, the frequent occurrence of remissions and the negative anatomic observations. Goldflam pointed out that the functional changes in the muscles were due to muscle exhaustion rather than to paralysis of the muscles. Jolly, in 1894, investigated the nature of this muscle fatigue and his work led to the discovery of the so-called "Jolly" or "myasthenic" reaction.

In 1900 Weigert [2] published the report of a case in which he described lymphocytic infiltrations into the muscles, which Buzzard [3] (1905) named lymphorrhages.

Incidence

Keschner and Strauss [1] stated that up to 1928 more than 300 cases had been reported. The disease apparently affects females more often than males, occurring most frequently between the ages of 20 and 50 years. Booth records one case at 23 months, the oldest in his series of 250 cases being 70 years. The commonest age of onset is recorded as the third decade, its onset before puberty being rare.

Etiology

Possibly acute infectious diseases are exciting causes. The condition has been described as following influenza, typhoid fever, diphtheria, scarlet fever, and acute articular rheumatism. A number of the cases have been associated with pregnancy.

* Read before the General Medicine Section of the California Medical Association at the sixty-second annual session, Del Monte, April 24–27, 1933.

Symptomatology

Beginning insidiously, the disease usually runs a chronic course with remissions and exacerbations, especially in the early stages. There is an abnormal exhaustibility of the muscular system. In about two-thirds of the cases the order of involvement of muscles is as follows: First, the ocular muscles, characterized by a ptosis of the lids and a diplopia; second, the laryngeal muscles with dysphagia and difficulty in phonation due to a weakness of the vocal cords. There is a disturbance in the muscles of the face and lips, lending to the countenance the so-called nasal smile; later on the muscles of the extremities and the trunk may become involved. Any of the voluntary muscles may become affected. The tendon reflexes generally are normal, though they may disappear following repeated percussion taps, to return to normal again after a few minutes' rest. Sensory disturbances are usually absent. Generalized pains, headaches and a feeling of stiffness, especially in the facial muscles, may occur. The diagnosis is made from the ptosis, the facial expression, the nasal speech, the rapid fatiguability of muscles, the absence of atrophy and tremors and the remarkable variations in severity of symptoms. The outstanding diagnostic factor, of course, is the fact that symptoms are aggravated by exertion and improve upon rest. The myasthenic reaction of Jolly is the rapid exhaustion of muscles, by faradism, not by galvanism.

Prognosis

Cases have been reported terminating fatally in as short a time as 14 days, though remissions are so common that they are almost regarded as a typical feature of the disease. Remissions may be as long as 18 years. Various authors have stated that one-half the cases die within six months from the time of onset, death resulting from exhaustion of the muscles of respiration or from choking as a result of the inability to swallow. The majority of cases die within a year.

Pathology

Buzzard [3] described lymphorrhages as occurring in more than 50 per cent of cases. Weigert [2] regarded these collections of cells in the muscles as metastases from the thymic tumor which he described in his case. In 1917 Bell [4] collected 56 cases with autopsy findings, 17 of which showed enlargement of the thymus. Bell was inclined to classify the thymic tumor which he found in his case as a benign thymoma, it being composed of thymic tissue of a fetal type. Starr [5] in 1912 reviewed 250 cases of myasthenia gravis and noted that a pathologic condition of the thymus was recorded in 28 per cent of the cases that came to autopsy.

Treatment

Inasmuch as myasthenia gravis is a disease of unknown etiology and one in which the underlying pathologic condition is as yet but poorly understood,

therapeutic measures of necessity must be grossly empirical. As in other conditions where there are long remissions and exacerbations of symptoms, the efficacy of therapeutic measures must be judged with the possibilities in mind not only of purely psychic benefit, but also of the fortuitous occurrence of improvement as the result of a remission in the disease. These factors indeed make the evaluation of the results of therapy difficult. Of paramount importance as therapeutic measures are complete physical and mental rest and relaxation, and the maintenance of nutrition. Because of the frequent dysphagia due to involvement of the muscles of deglutition, tube feeding often may have to be resorted to. Recalling the very nature of the disease, it would seem quite apparent that all forms of exercise, massage and faradism are not only useless but definitely contraindicated.

No detailed recitation of the various therapeutic measures that have been employed in the treatment of myasthenia gravis will be attempted. Suffice it to say, in summary, that the principal drugs that have been tried are the arsenicals, strychnine, the various endocrine products such as thyroid, parathyroid and suprarenal substances, the administration of calcium, and the injection of thorium. Furthermore, because of the possible significance of the finding of an enlarged thymus in a fairly large percentage of cases, thymectomy, or roentgen-ray exposure to the thymus, has been employed in several cases with variable success.[7]

A therapeutic measure which should not go unnoticed is the use of ephedrin, as reported by Edgeworth [7] in 1930. That author, herself a victim of myasthenia gravis, reports the very encouraging results of her experiences with the use of ephedrin, stating that while taking a dosage of 3/8 gr. of ephedrin twice daily for an entirely different purpose, she noticed marked improvement in the myasthenic symptoms.

My interest in the subject of myasthenia gravis was stimulated by the recognition of the disease in a case that I was called in to see in August 1932. Coincidentally, one of my colleagues, Dr. William Van Dalsem, has had a similar case. The origin of the symptoms in both cases dated from about the same time. With Dr. Van Dalsem's kind permission, I shall relate the chief points of interest in both these cases.

Case I

Mr. O. F. H., male, age 56, born in California, a rancher, married. His wife and four children are living and well. His family history is negative. Past history: Pneumonia in 1915, and in 1918 an influenzal attack which was complicated by severe headaches, but from which he entirely recovered quite promptly. He has had frequent attacks of tonsillitis. The history of his present illness elicited on my first visit was as follows:

Principal complaint: Weakness, dysphagia, difficulty in talking and ptosis of both upper eyelids. His history reads somewhat as follows: While in the east in June 1931, on an occasion when he was walking on the street, he noticed a haze coming across his eyes which lasted only for an afternoon. In August 1931, he had what he called indigestion characterized by some abdominal cramps, to which he attached no particular significance. In January 1932, he had an attack of severe tonsillitis with

backache. The first indication of his present difficulty began in May 1932, when he noticed a ptosis of the right lid of a few hours' duration, which had entirely disappeared by the following morning.

On May 15, 1932, while driving his car, he suddenly noticed a drooping of the left upper lid which caused him to squint. Then a haze came over the eyes which was so marked that he had to turn the wheel over to his wife. He was at once placed in the hospital, where a complete physical examination revealed no evidence of abnormalities in the blood, urine or spinal fluid. No definite diagnosis was arrived at. Symptoms of ptosis and transitory diplopia continued. The first difficulty in swallowing was noted about June 15, one month after the onset of symptoms, and was characterized by tightness in the throat. Thinking that the condition might be due to some focal infection, a tonsillectomy was performed in June, and during July all the upper teeth and a few of the lower, 14 in all, were extracted. These procedures, however, were followed by little, if any, improvement.

Upon my assuming charge of the case, further studies showed a blood count of RBC 5,330,000; Hgb 80 per cent (Dare), 88 per cent (Tallquist); WBC 6,700; with normal differential. Serum calcium was 11.8 mg. per 100 c.c. blood. The basal metabolic rate was minus two. Roentgen-ray of the chest showed no evidence of mediastinal enlargement.

A diagnosis of myasthenia gravis was made. Accordingly, we began twice daily injections of 1 c.c. of the adrenal cortex preparation, Eschatin, as elaborated by Swingle and Pfiffner. On successive days, for 10 days, this man was given 2 c.c. Eschatin daily. We noticed a rise in blood pressure from 140/90 to 170/110. My notes show that he considered that he was perhaps slightly "pepped up" by this procedure.

Coincidentally, because of Pemberton's [8] observation on the increased elimination of calcium in this disease, we began the administration of calcium gluconate in doses of a half ounce three times daily. Cod liver oil, one dram three times daily, and strychnine, grains 1/60 three times daily, were also given. The patient continued to have increasingly more difficulty in swallowing. In fact, he became quite panicky upon even the thought of having to take food, and therefore about September 1, 1932, we began to feed him through a duodenal tube. He was given a well-balanced diet of 2250 calories of such consistency that it could easily be given him through the tube. The patient was kept closely confined to his bed to conserve his strength.

Case II

H. S. K., age 56, male, married, wife never pregnant. Patient has always enjoyed excellent health with the exception of the usual childhood diseases. The present history began in June 1932, when the patient rather suddenly developed a ptosis of the lid of one eye and within a week of that, the other eye. This was followed a week later by weakness of the extra-ocular muscles with limitation of movement of the right eyeball in all directions, and a coincident development of a diplopia. There was quite prompt improvement in the ptosis of the lids, and within a three-week period, during which he was taking doses of 1/30 of a grain of strychnine three times daily, the ptosis cleared up entirely though there was little improvement in the ocular muscles. In August the patient gradually developed a dysphagia to the extent that he could take only soft foods and liquids. He complained also of fatigue on talking, though the speech difficulty was not apparent to anyone save the patient. There was little involvement of the facial muscles, though the patient often remarked that he had an abnormal smile which did not feel natural to him. He was always able to whistle. There was very little loss of weight; but considerable insomnia, much nervousness and depression were marked. The Wassermann was negative. The basal metabolic rate was minus twelve. A roentgen-ray of the chest was negative.

At a time when the outlook for our cases seemed quite hopeless, there came to our attention reports from The Mayo Clinic by Boothby [9, 13] and his co-workers on the effect of the use of the amino acid glycine, or glycocoll, in the treatment of myasthenia gravis.

Milhorat, Techner, and Thomas [10] investigated the effect of the administration of glycine in progressive muscular dystrophy, pointing out that patients with that disease show a creatinuria which was maintained even on a creatin free diet, and that in contradistinction to the normal subject they excrete ingested creatin almost quantitatively, and that this inability to retain ingested creatin is in proportion to the severity of the disease. They found that the daily ingestion of 5 grams of glycine was followed by a definite rise in creatinuria, and that 15 to 20 grams daily increased the daily excretion of creatin 300 to 500 mg., the more advanced cases excreting the larger amounts. After a period of weeks, depending on how advanced the case was, the creatinuria began to decrease despite the continuance of glycine until it fell to the former control level. In some cases this required two to three weeks. The time required for improvement varied widely. One patient showed a marked improvement in three weeks; in another, no definite increase in muscle function could be demonstrated at the end of nine weeks, although there was much subjective improvement. Two patients who showed considerable improvement after glycine were permitted to interrupt the treatment for three months. The improvement continued for three or four weeks and then gradually disappeared, until their condition returned to its previous status. One of these patients was again placed on glycine and showed the same remarkable improvement in the same muscle groups as before.

Likewise, Beard and Barnes [11] studied the influence of feeding amino acids upon the creatin-creatinine metabolism. They fed healthy rats with various amino acids, among them glycine, and concluded that all amino acids of the protein molecule studied have the power of increasing the normal creatin content of young rat muscle. This process is fairly rapid, reaching its maximum within 17 to 24 hours after ingestion of the amino acid. Also, they studied the effect of the various amino acids upon creatinine elimination in the urine of rats. From this experiment they concluded that the feeding of any of the amino acids caused an increase in the creatinine output in the urine, this increase being greatest after feeding glycine. Then they studied the influence in man of the ingestion of various proteins and amino acids, among which was glycine, and found large increases in the excretion of creatinine, but they are of the opinion that the feeding of proteins or amino acids as such in large quantities for one day usually gives the largest increases in creatin formation and in creatinine excretion. In muscular dystrophies Beard and Barnes found that glycine caused a 40 per cent increase in creatinine elimination, and they found that the feeding of gelatin, and to a lesser extent edestin, had much the same effect. They are of the opinion that possibly the ingestion of the amino acids caused an increased formation

of creatin in the muscles and increased elimination of creatinine in the urine. Luck [12] showed that the feeding of glycine to rats caused an increase in the amino acid content of muscle.

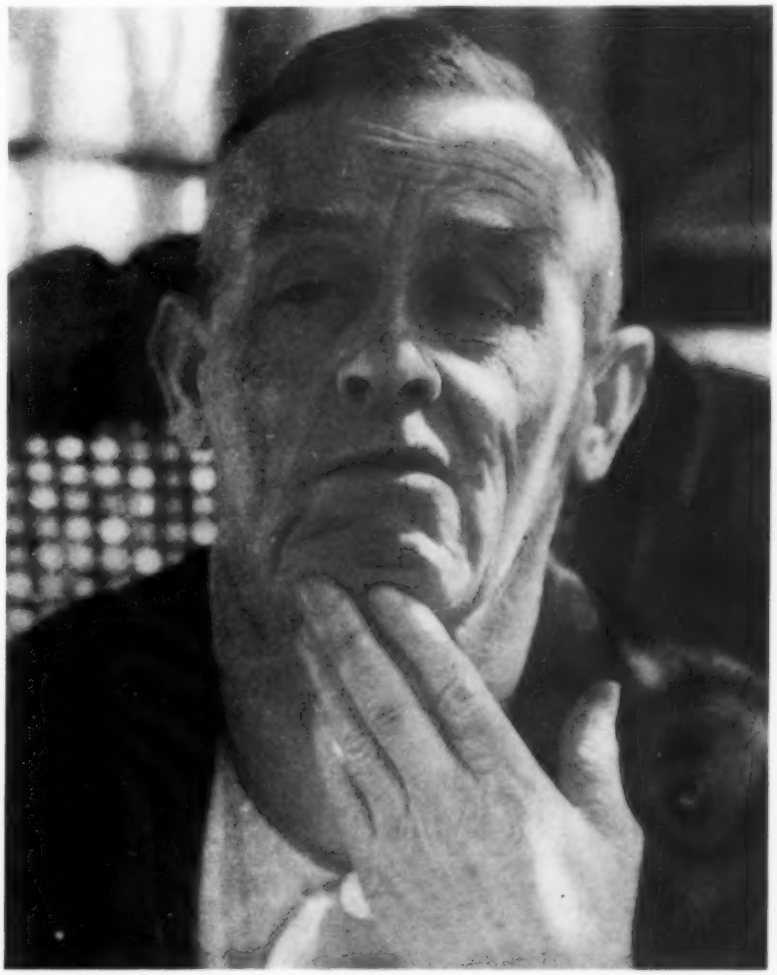

FIG. 1. *Case I.* One month after the institution of glycine therapy. Note the persistent bilateral ptosis. The weakness of the masseters is well illustrated by the fact that the patient was forced to support the lower jaw with the hand.

THE USE OF GLYCINE IN OUR PATIENTS

Case 1 was placed on glycine administration on October 25, 1932. From that date up to the present he has been on a constant dose of 15 grams twice daily.

Case 2 began taking glycine in doses of 20 grams twice daily on October 30, and continued on that dosage up to February 15, 1933, since which time he has been on a dosage of 15 grams twice daily. Neither patient has ex-

perienced any difficulty in taking the drug. Simultaneously, both of these patients, since November 1, 1932, have been taking ephedrin sulphate daily in dosages of 3/8 gr. twice daily up to January 20, 1933. From January 20 to date case 2 has taken ephedrin sulphate in dosages of 3/16 gr. twice daily. From January 20 to March 20, 1933, case 1 took that dosage (3/16 gr. twice daily) but since that date he has returned to gr. 3/8 twice daily. He believes that on this latter dosage he feels stronger.

The subsequent progress of our cases can be best summarized as follows:

FIG. 2. *Case I.* Taken after five months of continuous daily glycine administration.

CASE I

October 25, 1932, when glycine administration was instituted, the patient weighed 127 pounds. By March 20, 1933, he weighed 156 pounds. This gain in weight and strength can best be illustrated by photographs (figures 1 and 2). Within one week after beginning glycine, the ptosis of the lids had become much less marked, the patient was drinking milk from a glass, and he was walking about daily. By the end of the third week, he ate an entire meal without the tube. He discontinued the use of

the duodenal tube entirely on January 24, 1933 (two months after commencing glycine therapy). Since then his progress has been most satisfactory. He is up and about all day and goes about his duties of managing a fruit ranch, feeling perfectly strong.

Case II

The patient began taking glycine, 20 grams twice daily, and ephedrin sulphate, gr. 3/8 twice daily, on October 30, 1932. There was prompt improvement in swallowing within two weeks, with slight improvement in the condition of the extra-ocular muscles.

During the month of February 1933, the patient took 15 units of insulin twice daily (before his morning and evening meals) with resultant gain of an appreciable amount of weight.

On December 8, 1932, this patient had recovered sufficiently to return to his work as an executive in a public utilities office, at first for two to four hours a day, and since February 1, for four to six hours daily.

From about January 1 to February 15, the improvement in the condition of extra-ocular muscles was about at a standstill. By March 31 all symptoms had practically disappeared. The impairment of the extra-ocular movements of the left eye had entirely cleared up. There persisted slight limitation of external rotation of the right eye.

Laboratory Studies

Because of the fact that various investigators had noted changes in the creatin-creatinine metabolism in the various muscular dystrophies, it seemed

Chart I

Urinary findings in case 1. Administration of 15 grams of glycine twice daily was instituted 10–25–32

Day	Date	Urinary Output per 24 hrs. in c.c.	Urinary Preformed Creatinine in gm. per 24 hrs.	Urinary Preformed Creatinine-Nitrogen in gm. per 24 hrs.	Urinary Creatine in gm. per 24 hrs.	Urinary Creatine-Nitrogen in gm. per 24 hrs.	Creatin-N_2 to Preformed Creatinine-N_2 ratio
	10–24–32	2580	.786	.291	.976	.312	1.07 : 1
1	10–25–32	(Treatment started)					
2	10–27–32	1530	1.243	.461	.066	.021	.04 : 1
4	10–28–32	1740	1.374	.509	.632	.202	.41 : 1
5	10–29–32	2150	1.367	.507	.273	.087	.17 : 1
6	10–30–32	3160	1.753	.650	.382	.122	.18 : 1
7	10–31–32	2450	1.949	.723	.121	.038	.05 : 1
8	11–1–32	2960	2.184	.810	.816	.261	.32 : 1
9	11–2–32	2830	1.519	.563	000	000	—
10	11–3–32	2310	1.374	.509	.041	.013	.02 : 1
11	11–4–32	2980	1.645	.610	000	000	—
12	11–5–32	2730	1.578	.585	.096	.030	.05 : 1
13	11–6–32	1790	1.491	.553	.181	.057	.10 : 1
14	11–7–32	2535	2.535	.940	.051	.016	.01 : 1
15	11–8–32	2330	2.008	.744	.072	.023	.03 : 1
23	11–15–32	3730	4.515	1.675	.086	.027	.01 : 1
37	11–29–32	2610	1.652	.612	.096	.020	.03 : 1
52	12–13–32	2200	2.010	.745	.906	.289	.38 : 1
164	4–4–33	1000	2.222	.824	.050	.001	.001 : 1

CHART II

Urinary findings in case 2. Administration of glycine was instituted 10–30–32

Day	Date	Urinary Output per 24 hrs. in c.c.	Urinary Preformed Creatinine in gm. per 24 hrs.	Urinary Preformed Creatinine-Nitrogen in gm. per 24 hrs.	Urinary Creatin in gm. per 24 hrs.	Urinary Creatin-Nitrogen in gm. per 24 hrs.	Creatin-N_2 to Preformed Creatinine-N_2 ratio
	10–21–32	1645	1.587	.588	.385	.123	.20 : 1
1	10–31–32	1100	1.782	.611	.115	.036	.05 : 1
2	11–1–32	1430	1.778	.659	.397	.127	.19 : 1
3	11–2–32	1340	1.660	.615	.201	.064	.10 : 1
4	11–3–32	980	1.410	.523	.162	.051	.09 : 1
5	11–4–32	1330	1.673	.620	.380	.121	.19 : 1
6	11–5–32	980	1.590	.589	.170	.054	.09 : 1
7	11–6–32	795	1.413	.524	.071	.022	.04 : 1
8	11–7–32	850	2.210	.819	.119	.038	.04 : 1
9	11–8–32	1100	1.826	.677	.002	.0006	.009 : 1
10	11–9–32	1350	1.487	.550	.135	.042	.079 : 1
11	11–10–32	1850	2.053	.761	.153	.048	.064 : 1
12	11–11–32	1290	1.775	.658	.112	.035	.054 : 1
13	11–12–32	910	1.598	.592	.051	.016	.02 : 1
14	11–13–32	1500	2.406	.892	.180	.057	.06 : 1
15	11–14–32	1400	1.497	.555	.150	.048	.08 : 1
16	11–15–32	1640	2.486	.922	.075	.024	.02 : 1
17	11–16–32	1570	2.264	.839	.153	.048	.05 : 1
18	11–17–32	1160	1.698	.629	.056	.017	.02 : 1
19	11–18–32	885	2.100	.779	.081	.025	.03 : 1
20	11–19–32	1050	2.142	.794	.069	.022	.02 : 1
21	11–20–32	950	2.658	.986	.000	.000	
22	11–21–32	1190	3.236	1.200	.423	.135	.1 : 1
23	11–22–32	1730	2.92	1.08	.128	.040	.03 : 1
24	11–23–32	1080	2.41	.894	.071	.022	.02 : 1
32	12–1–32	1680	1.788	.663	.018	.005	.008 : 1
40	12–8–32	850	1.481	.549	.114	.036	.06 : 1
48	12–15–32	950	2.405	.892	.078	.024	.02 : 1
56	12–22–32	1200	1.592	.590	.151	.048	.08 : 1
64	12–29–32	1420	1.489	.552	.239	.076	.14 : 1
72	1–5–33	1050	1.369	.507	.245	.078	.15 : 1
162	4–4–33	1660	1.980	.734	.217	.069	.09 : 1

advisable to make observations on the creatin-creatinine output in the urine on our patients while on glycine administration. One object of these studies was to determine whether or not there was a parallelism between the excretion of these nitrogenous products and the clinical course of the disease. Charts 1 and 2 record these findings in cases 1 and 2 respectively.

It will be noted that the first line of figures to appear across the top of the charts are the findings before the administration of glycine was begun. Recorded in the chart on each of the test days are the total daily urinary output, the preformed creatinine and creatinine-nitrogen, and the creatin and creatin-nitrogen in each 24 hour urinary output. At the extreme right

will be found the creatin-nitrogen to preformed creatinine-nitrogen ratio.

It is well appreciated that these patients were not on a strictly constant diet from day to day, and no doubt the dietary factor has its influence in upsetting the accuracy of these figures. However, in case 1, because of the fact that he was tube fed for almost two months before glycine treatment was instituted, I feel that his diet was kept fairly constant and under control from day to day, and so at least in case 1 the figures should be of some value. Both cases 1 and 2 took fairly large amounts of gelatin daily in order to avail themselves of that source of glycine.

Comments on Laboratory Studies in Case I

The feeding of glycine seemed to have a variable diuretic effect in case 1. The creatin-nitrogen to creatinine-nitrogen elimination ratio previous to beginning glycine was 1.07 : 1, the lowest ratio during the first 13 days during which the patient was on glycine was 0, and the highest .41 : 1, with an average of .106 : 1. The 24 hour output of preformed creatinine-nitrogen on the day before glycine was begun was .291 gm. The value for creatin-nitrogen in the same specimen was .312 gm. During the first 13 days of glycine administration the range of 24 hour urinary excretion of preformed creatinine-nitrogen was between .507 gm. on the second day to .940 gm. on the twelfth day. On glycine, the average excretion of preformed creatinine-nitrogen was .628 gm., while the creatin-nitrogen during the same period on the same specimens ranged from a value of zero to a maximum of .261 gm. on the sixth day, the average being 0.066 gm. during this first 13 day period.

The total creatinine eliminated in the urine per 24 hours reached its maximum on the nineteenth day on glycine when 4.51 grams were eliminated, with a ratio of creatin-N_2 to preformed creatinine-nitrogen at 0.03 : 1. After 48 days of glycine therapy the ratio of creatin-nitrogen to preformed creatinine-nitrogen was .38 : 1, and the creatinine eliminated had dropped to 2.01 gm. while the creatin had jumped to its highest figure of .906 gm. The chart shows that on the one hundred sixty-fourth day on glycine the creatin-nitrogen to the preformed creatinine-nitrogen ratio had fallen to .001 : 1.

Case II

The diuretic effect following the use of glycine was not noted as in case 1. Prior to the commencement of the treatment the creatin-nitrogen to creatinine-nitrogen ratio was 0.2 : 1. That ratio fell to its lowest level on the ninth day following the institution of glycine therapy, and was at its maximum on the second day when it was .19 : 1 (this same level was reached on the fifth day of glycine administration). The average ratio during the first 23 days, during which time daily urinalyses were made, was .06 : 1. The 24 hour output of preformed creatinine-nitrogen on the day previous to commencement of glycine was .587 gm. The value for creatin-nitrogen in the same specimen was .123 gm.

During the first 23 days of glycine administration the range for 24 hour urinary excretion of preformed creatinine-nitrogen was between .524 gm. (on the seventh day) to 1.2 gm. on the twenty-first day, the average for the 23 days being .74 gm. The range of the urinary creatin-nitrogen for the 23 day period was from a minimum of no detectable trace on the twentieth day to a maximum of .135 gm. on the twenty-first day, the average being .455 gm.

The total preformed creatinine eliminated in the urine in 24 hours reached its maximum of 3.236 gm. on the twenty-second day, on which day .423 gm. of creatin was eliminated. Chart 2 will indicate that on the sixty-fourth day of glycine administration preformed creatinine elimination in 24 hours was 1.489 gm. The creatin was .239 gm. and the ratio of the creatin-nitrogen to preformed creatinine-nitrogen was .15 : 1. On the one hundred sixty-second day on glycine the ratio of creatin-nitrogen to preformed creatinine-nitrogen was .09 : 1.

Summary

1. Two cases of myasthenia gravis, both in males in the sixth decade of life, have been presented.

2. Both cases have shown very definite and striking clinical improvement, on a combination treatment of ephedrin sulphate and the amino acid, glycine.

3. Studies are presented of the elimination in the urine of the creatin and creatinine, together with the preformed creatinine-nitrogen and creatin-nitrogen, and the ratio of the creatin-nitrogen to the preformed creatinine-nitrogen.

(*a*) In the two cases presented, the administration of glycine was accompanied by an increase in the elimination of creatinine and preformed creatinine-nitrogen.

(*b*) The maximum output of creatinine-nitrogen occurred on the twelfth day in case 1, and on the twenty-second day in case 2. The average excretion during the test period in case 1 was .628 gm., and in case 2, .74 gm.

(*c*) In the two cases there was a definite drop in the excretion of the urinary creatin-nitrogen from a value in case 1 of .312 gm. (before test) to daily average excretion of .066 gm. for the test period of 13 days. In case 2 this decrease was from .123 gm. before the test period to a daily average excretion of .045 gm. per day (period of 23 days).

(*d*) The ratio of the creatin-nitrogen to preformed creatinine-nitrogen in both cases fell under glycine administration, in case 1 from a ratio of 1.07 : 1 to an average ratio of .106 : 1. In case 2 this ratio fell from one of .2 : 1 to one of .06 : 1.

4. A dosage of 15 grams twice daily of glycine is an effectual dosage, and is probably the optimal dosage.

5. Ephedrin sulphate seems to augment the efficacy of the glycine. In our experience a dosage of 3/8 gr. twice daily given about 20 minutes after the dose of glycine is the optimal dosage. This dosage seems superior to a small one of 3/16 grains.

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THE PERNICIOUS TYPE OF NERVOUS DYSPEPSIA *

By EDWARD C. KLEIN, JR., M.D., F.A.C.P., *Newark, New Jersey*

THAT there is such a nosological entity as nervous dyspepsia is generally admitted. It constitutes a large proportion of the practitioner's clinical office material. The real difficulty begins when an attempt is made to define it. Alvarez in his classic book, *Nervous Indigestion,* describes it as a convenient term by which to designate all those gastrointestinal disturbances for which no organic cause can be found. Leube thought that the symptoms of nervous dyspepsia depended on a morbid supersensitivity at the beginning of digestion of the gastric nervous mechanism. He believed that to make the diagnosis it was necessary to exclude not only anatomical changes but even functional disturbances of secretion and motility of that organ. He stressed the importance of the discrepancy between the multitude of subjective complaints and the lack of objective findings in the stomach. A test dinner was to be given, and if the stomach were empty seven hours later then the symptoms were due to nervous dyspepsia. This viewpoint did not go unchallenged, however, for Beard, Rockwell and Ewald opposed it, holding that the symptoms of nervous dyspepsia were merely manifestations of fatigue, hysteria or anxiety states. On the other hand, there is the clinical fact that anatomical lesions often exist for a long time without symptoms but sooner or later unleash the syndrome of nervous dyspepsia. Some of such lesions may be cited, for example Oertner's syndrome in early arteriosclerotic disease of the vessels of the stomach, gastric crises in early and atypical tabes, plexitis of the solar plexus as a residuum of a previous infection, larvated ulcer, gall-bladder, appendiceal or pancreatic affections, or even visceroptosis.

A modern physiologic concept, advanced by Ivy in particular, is that there is a cephalic, gastric and intestinal phase to the digestive cycle. Therefore, a disturbance of any one of these factors may be responsible for dyspeptic symptoms; and to limit the concept of nervous dyspepsia entirely to the stomach may involve an error of localization. While it must be admitted that the problem of the causation of this disorder belongs to the realm of psychiatry, the continued operation of the corrosive action of emotion brings about somatic effects, which may call for all the resources of diagnosis and therapeusis before any recovery can be expected.

This remark applies with special force to the class of cases which I have named the pernicious type. The frequency of visceroptosis with its mechanical drag on the local nervous system, thus initiating the complaints and distress, has been noted by many observers, especially Stiller. Yet he also saw that something more than a mere mechanical displacement and tug was necessary to account for the ailments attending this state. He, therefore,

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added the concept of constitutional weakness (asthenia congenita) by which he meant to include psychic and emotional instability as well as the mechanical defects. Dubois claims that 90 per cent of all dyspeptics are psychoneurotics. The work of Cannon and others has shown that hormonal influences are associated with these psychic factors. It is questionable indeed whether nervous dyspepsia ever occurs as a purely functional state in the sense that Leube conceived. The complexity of the whole matter is due to the mutable and bizarre manifestations of personality variations. Certain definite patterns, however, are presented just as in other psychoneuroses. Thus either aerophagia, peristaltic unrest, rumination, anorexia, or persistent vomiting may be the outstanding symptom in an individual case. It is these latter two complaints that are the characteristic feature of the pernicious type of nervous dyspepsia.

We find a variable number of factors, any one of which may dominate the situation in nervous dyspepsia. I believe that some sort of schema is desirable in order to facilitate the recognition of the different types met with in practice. The following classification has served me satisfactorily:

1. Cases of purely psychic origin which remain without extension to the periphery, i.e., the pure hypochondriacal type.

2. Cases, neurogenous in origin, in which a local defect resulting from toxic substances, fatigue, infection, trauma or autogenesis is attended by centripetal extension.

3. Cases of psychic causation with centrifugal extension and centripetal repercussion.

4. The psychoses with delusions in reference to the alimentary system.

The threshold and intensity of reaction vary unceasingly even in the same individual; and they may be much influenced by the inhibiting effect of habit and education. Much of education is simply for the purpose of inhibiting reflex action and the somatic manifestations of psychic operations. Consequently, at the onset we must visualize the clinical picture as a shifting and kaleidoscopic drama. In addition, the pathologic pattern is often influenced or even transformed by additional environmental circumstances and secondary psychogenous factors. Therefore as soon as psychic causation is discovered, the mechanism of the psychic patterns must be studied, but without neglecting to investigate the physiologic and morphologic changes as well. For therapeutic purposes, these patients may be divided into the mild and, what experience has obliged me to designate as the "pernicious" cases of nervous dyspepsia.

The mild case, with its feeling of epigastric fulness, borborygmus, pyrosis, palpitation, abdominal distention, dizziness and headache, weakness of memory, cold hands and feet, anxiety relieved by the passage of flatus or the belching up of gas, its ribbon stools or scybalous feces, can usually be corrected by adjusting environmental circumstances and securing the control of the remaining psychoneurotic residuum. These cases do not die, but they are often prevented from following their normal mode of life.

Their fears of certain foods and similar phobias, and their interminable and reiterated complaints cause such annoyance to others that their home life is frequently ruined. The antagonistic family attitude reacts again on the patient; and this vicious circle results in such an aggravation of the condition as often to render it practically incurable. To tell such individuals that they are suffering from an over active imagination is not only imprudent but wrong. The medical attendant must remember that he is dealing with hypersuggestible material, weak in will, strongly influenced by emotion and not by reason. Such patients are often impatient, vacillating and hard to hold. Confidence is of prime importance and the most effective therapy is that which solves the psychic problem.

It is not intended here to discuss further these cases, nor the psychotic types of patients. What has urged me to choose the term "pernicious" in this paper is my concern for those cases of anorexia nervosa and vomiting which run a more or less malignant course and present a very grave prognosis.

The four cases that I present were all women in the third decade of life, and two of the four died.

Case I

The patient was a private secretary who fell in love with her employer. It seems that he was unaware of this and quite suddenly married another woman. On learning the news, she lost her appetite and died 11 months later of extreme inanition. An autopsy was negative except for the incidental findings of inanition.

Case II

A married woman, of extreme visceroptotic habitus, was told by her medical attendant that she had a positive Wassermann and subsequent investigation proved that her husband, to whom she was deeply attached, was the causative agent. Her romance was shattered and she went out to work determined to rid herself of her infection. Repeated serologic tests were negative, yet the phobia of a social disease was too strong to be suppressed. Esophagism soon developed, then sitophobia and eventually vomiting. This became so pernicious that ultimately nothing was retained. Emaciation developed to the degree of marasmus. A surgeon came in on the case and performed a gastroenterostomy on the theory that there was enough duodenal kink to justify it. The symptoms persisted, and even became worse. Several months later the patient died of inanition.

Case III

The third patient was a woman who developed severe nervous anorexia and aerophagia with vomiting as a result of a severe sorrow. Complete aversion to food in any form resulted in extreme emaciation and bedsores. Duodenal alimentation was resorted to and the tube left well into the jejunum to prevent retrostalsis from bringing the liquid food into the stomach. After five months of difficult intubation, during which time death often seemed imminent, the patient recovered; but only because the time element succeeded in bleaching out the psychic factor.

Case IV

The fourth case was a young woman who had undergone four abdominal sections for adhesions following a pus appendix operation. The resultant invalidism from

the procedures broke up a tentative engagement, her fiancé bluntly telling her she was too sickly to marry. Her chagrin at this rebuff actually improved her temporarily, and plans to marry a rival suitor whom she did not love were nearly completed. They were only thwarted by an attack of repeated vomiting, no food being retained at all. Anorexia and inanition rapidly set in until the patient fell to 67 pounds, her original weight being 140 pounds. Duodenal alimentation was attempted several times. It was rejected once by the patient who was quite resigned to die. A second trial resulted in the tube being vomited up and ultimately several intubations at short intervals of three to four weeks were successful. More than a month of continuous intubation invariably caused diarrhea. Over a year passed with little or no improvement, the tubal feeding alone keeping her alive. Two hospitalizations for study and consultative opinions yielded negative results. Roentgen-rays of the chest and gastrointestinal tract were negative. The basal metabolic rate was minus 18 and minus 22. Gradually the psychic trauma lessened, symptoms abated slowly and mouth feedings were stepped up to a rational intake. She ultimately reached 100 pounds, was able to be up and around, and 18 months later married the man of her choice who proved to be neither of the two former suitors. Although she showed a persistent amenorrhea for a year and a half, she eventually became pregnant and was delivered of a normal full term baby boy at St. Barnabas Hospital. She is well and happy today, weighing 155 pounds.

The remarkable thing about all these cases is, as Venables says, that no matter what the psychic cause may be, the complaints center entirely around food. Clow quotes Dejerine's statement that he has never seen a patient recover who loses more than half her weight. This observation is affirmed in the two fatal cases here cited. Another notable point is that a psychoneurotic heredity was absent in all these cases. Although all my cases were women, the literature, though scanty, shows that males are affected also. Berkman of The Mayo Clinic has given the most exhaustive analysis of any, reporting 117 cases, 28 of whom were males. Gull's three cases and 45 of Berkman's cases had amenorrhea. Cases 2 and 4 of mine had amenorrhea. Most of Berkman's cases had a lowered basal metabolic rate. My last case showed a minus 18 but neither thyroid nor suprarenal extract proved of any therapeutic value. Leede has indicted the suprarenal as the site of the chief endocrine disorder but this does not seem to be substantiated. Pain is rarely complained of and none of my cases exhibited this symptom. As soon as inanition sets in the pulse is slow and the blood pressure is low. Except for ptosis in case 2 the roentgenograms were negative. Gastric analysis in the early stages showed no abnormalities, but hypoacidity tends to develop with terminal exhaustion. Fecal tests were negative except for hemorrhoidal blood in one.

Diagnostically, the mild cases are distinguished by their lability of symptomatology. It is characteristic that the patient presents symptoms which do not fit within the bracket of the known diseases. The feeling of fulness and aerophagia may suddenly change to pyrosis, dizziness and headache with confusion and numbness of the extremities or tongue. But curiously, the pernicious type is stigmatized by the stability of symptoms. They begin with anorexia or vomiting or both and remain so until recovery or

death intervenes. The roentgenologic processes of duodenal stasis or reversed peristalsis as seen fluoroscopically continue with little change until convalescence ensues. Vomiting in the normal individual is a physiologic act usually preceded by more or less severe nausea and pallor with varying degrees of perspiration, weakness and confusion. In the pernicious type of nervous dyspepsia nausea is slight or absent. If present, it is of short duration unaccompanied by somatic perturbation and with no cold sweats or pallor. The patient shows, moreover, that the successive repetition of emesis develops a greater facility and ease of vomiting. Since nervous dyspepsia may, and so often does, accompany organic disease, all the probable organic affections must be excluded before risking the diagnosis of nervous dyspepsia of the uncomplicated type. Even at that, one cannot predict during the early stages which of his cases will run a benign or a pernicious course. As to the mechanism, one is impressed with what seems to be an inversion of vitality and an annihilation of the pleasure of life. Berkman epitomizes the long drawn out duration as follows: The loss of appetite following a certain psychic trauma is followed by inanition and consequent low rate of metabolism. This lowered rate appears to be a protective mechanism, for the tissues would be rapidly consumed and death more frequent than it is, if the rate were higher.

When treatment of the pernicious case is considered it must be remembered that all the ordinary methods are unsuccessful. It is useless to discuss the psychic trauma at first, as the prime indication is to prevent death. Intubation of the jejunum should be done at once. To put the bulb merely in the duodenum is to aggravate the case. Violent expulsive efforts frequently result with ejection of the tube and with the superadded symptom of nausea. It is because of the duodenal retrostalsis that the tube should be put well into the jejunum. In this way, hourly or two hourly feedings can be more readily tolerated and larger quantities of peptonized milk, with cream, lactose, egg and peptone additions, initiated. These feedings may be continued for a month or longer if necessary and may even have to be reinstituted if symptoms recur. When the tube cannot be tolerated on account of faucial irritation, or its passage will not be allowed by a refractory patient, the physician should not hesitate to have a jejunostomy done and kept open until recovery has occurred. Case 1 would have gotten well if this had been done, and case 2 should have had jejunostomy instead of gastroenterostomy. If tubal feedings alone do not control dehydration or acidosis, glucose by vein, skin or rectum may have to be resorted to.

The therapeutic use of insulin in stimulating appetite has been brought out by Bulatao and Carlson, Falta and recently by Nahum and Himwich. Berkman employed it in one of his cases but abandoned its further use because of lack of evidence of its effectiveness. It was attempted in case 4 but discontinued because of refusal of the mother to administer it. LaBarre's work demonstrates the reason for its failure in certain cases. Briefly, he showed that hypoglycemia initiated greater gastric muscular and

secretory action. Insulin by lowering blood sugar creates impulses in the brain which are conveyed by the vagus to the gastric musculature. These impulses increase peristalsis and this, reacting centripetally, registers in the field of consciousness as hunger. Accordingly, it can be inferred that insulin will be of service only in those cases in which it causes a hypoglycemia. Berkman claims that thyroid therapy is a valuable adjuvant measure because of the low basal rate. In spite of long continued use in case 4 it had only indifferent success.

When death has been prevented and inanition assuaged, then and only then comes the real time for psychotherapy. The removal of the psychogenetic factor, while of grave import, can not alone be counted upon to relieve the patient suffering from the serious type of this condition. Each case of pernicious nervous dyspepsia therefore must be considered from the individual standpoint.

To quote from S. I. Meltzer: "Lighter than air is psychotherapy. Do not practice it consciously. Have a thorough knowledge of your subject which entitles you to speak with conviction; have sincere sympathy which ought to manifest itself without obvious demonstration. Be practical in your advice and talk to the patient in common sense terms and you will have practiced psychotherapy honestly and successfully."

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HEPATIC COMPLICATIONS IN THE TREATMENT OF SYPHILIS

THE ROSE BENGAL TEST AS A MEANS OF DETECTING DISTURBANCES OF LIVER FUNCTION AND ITS USE AS A GUIDE IN THE THERAPY OF SYPHILIS *

By Gerson R. Biskind, M.D., Norman N. Epstein, M.D., and Wm. J. Kerr, M.D., F.A.C.P., *San Francisco, California*

Patients undergoing routine antisyphilitic therapy occasionally develop hepatic disturbances. The liver of the individual with syphilis may be damaged by the disease or by untoward effects of antisyphilitic remedies, or by a combination of both. Latent disease of the liver may also be found in certain patients undergoing specific treatment, in whom the usual methods of clinical examination fail to reveal these pathologic processes. The clinical recognition of the acute phases of hepatic disease offers little difficulty. After the subsidence of the acute process, however, the determination of the exact status of the liver requires careful study.

Rose Bengal Liver Function Test

Many methods have been devised to evaluate the functional capacity of the liver in order to obtain some evidence of its morphologic state. In the Out-Patient Clinic for Syphilis in the University of California Medical School the rose bengal dye test has proved to be a reliable and practical method of studying liver function for the past 10 years. The dye, di-iodo-tetra-chlor-fluorescein, is eliminated from the blood stream only by way of the biliary tract. The rate of disappearance of rose bengal from the blood stream is proportional to the excretory function of the liver in the absence of mechanical obstruction to the bile ducts. The dye is nontoxic in the dosage sufficient for the test. It does not deteriorate on standing or upon sterilization. It is inexpensive, readily obtainable, and is not irritating to the veins. It is rapidly excreted only by the liver, and the color remains unchanged in the body during the period of observation so that it is easily detected in the blood plasma or serum. It has a slight photodynamic action on red blood cells. For this reason the patient is instructed not to expose himself to bright sunlight within two or three hours after administration of the dye. This is especially important if the dye is retained in the circulation for more than the usual period. No severe reactions have been encountered by us except in two patients who went directly into bright sunlight following injection of the dye. In these cases an edema of the face occurred which persisted for several hours.

* Received for publication October 23, 1933.
From the Division of Dermatology, the Department of Medicine and the Department of Pathology, University of California Medical School, San Francisco.

The exact technic of the test has been described recently [1] and need not be repeated in detail here. It is sufficient to state that 10 c.c. of a 1 per cent aqueous solution are injected intravenously over a period of 30 to 40 seconds. Blood samples are withdrawn at two, eight and sixteen minutes after the injection. The dye reaches its maximum concentration in the blood stream approximately two minutes after administration. This two-minute specimen is used as the standard against which the eight- and sixteen-minute specimens are compared. This procedure eliminates the error that is encountered by the use of an artificially prepared standard. The comparison is carried out at present by means of a comparing spectroscope [1] which eliminates certain errors found in the colorimetric method. The presence of biliary pigments or other substances which interfere with the matching of colors is no longer a hazard. From experience in several hundred cases, a retention in the blood stream of less than 55 per cent of the dye at the end of eight minutes, and 35 per cent retention at 16 minutes is considered normal. Retention above these figures is abnormal and indicates an abnormal function of the liver. According to the findings observed by the use of this test, the cases will be designated as having a normal, slightly abnormal, or a definitely abnormal liver function.

In 1926 one of us [2] reported the results of a liver function investigation among a number of patients with syphilis using the rose bengal dye test. These patients were young adults, for the most part, with early syphilis. The results revealed: first, that latent hepatic disease could be detected by the test; second, that in patients who have developed arsphenamine jaundice the liver function may return to normal upon clinical recovery; and third, that an arsphenamine dermatitis is not always associated with a disturbance of liver function.

Other Liver Function Tests

In the past 10 years this field of investigation has attracted many workers. The determination of bilirubin in the blood stream by the van den Bergh method is generally used as an indicator of liver function. Chargin and Orgel,[3] Gerrard,[4] Dixon, Campbell and Hanna,[5] Irgang and Sala,[6] and others using this method feel that the presence of a latent jaundice indicates damage to the liver, and that intensive antisyphilitic treatment should be stopped when this is present, but may be resumed when the bilirubinemia returns to normal. Generally, it may be said that the determination of bilirubin in the blood will indicate the onset of an icterus, and thus warn against continuing arsenical treatment, but that it fails to demonstrate slowly progressing damage within the liver.

Greenbaum and Brown [7] used the phenol-tetra-chlor-phthalein dye test and found that a toxic icterus often leaves permanent dysfunction of the liver unassociated with clinical manifestations. Zieler [8] states that the determination of urobilinogen in the urine can be used as an indicator of liver function.

Present Investigation

The present investigation has been carried out upon patients in the Out-Patient Clinic for Syphilis at the University of California Medical School. For the most part they were older and had their infections for a longer period than the series reported in 1926. The investigation has the following objects:

First: To demonstrate latent liver dysfunction in the absence of clinical signs.

Second: To determine the degree of disturbance of liver function in patients with syphilis of the liver and to observe the effects of antisyphilitic therapy.

Third: To determine whether clinical recovery from an arsphenamine jaundice is always accompanied by complete return to normal of liver function.

Fourth: To determine the effect of long continued antisyphilitic therapy upon liver function.

Clinical Material

During the past three years the rose bengal test was performed upon 152 patients with syphilis. They were selected for study because they either were suspected of having hepatic involvement, or had developed jaundice at some time during the course of their treatment, or had been under antisyphilitic treatment for a long period of time.

Classification of Cases

Of the entire group, 102 were males and 50 were females. They were in the age groups shown by table 1. The greatest number were between

Table I

	Age Groups						
Years	10–19	20–29	30–39	40–49	50–59	60–69	70–79
Male	0	5	30	28	27	9	3
Female	1	9	10	16	14	0	0
Total	1	14	40	44	41	9	3

30 and 60 years of age. When grouped according to the diagnosis made at entry, 13 were in the primary stage of syphilis, 11 were in the secondary period, 71 were classified as latent, and 57 as late, 21 of these latter having some form of syphilis of the nervous system.

I. Untreated Group:

Eleven cases were examined with the rose bengal test before antisyphilitic therapy had been administered. Eight of these showed a normal rate of excretion of the dye and presented no clinical evidence indicating hepatic disease. The three abnormal cases had enlargement of the liver and are listed in table 2. In two cases (70 and 156) the liver function

TABLE II

Untreated Group; Syphilis of the Liver

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
70	51	M	Gummata of liver	8/10/31	81%	54%	Marked	Initial lesion in 1902. No antisyphilitic medication. Liver greatly enlarged and nodular. Following treatment with potassium iodide and bismuth there was marked clinical improvement. Left clinic.
				9/28/31	62%	50%	Moderate	
				12/22/31	67%	45%	Moderate	
128	40	F	Visceral syphilis	7/12/32	66%	50%	Moderate	Initial lesion in 1909, treated with several mercury rubs. Spleen greatly enlarged, almost to iliac crest. Large irregular liver. No reduction in size of organs after treatment with potassium iodide and intramuscular injections of mercury salicylate and bismuth. Splenectomy on 12/10/32. Pathologic diagnosis: syphilis of liver and spleen.
				10/ 7/32	65%	45%	Moderate	
				2/ 2/33	78%	52%	Moderate	
				3/21/33	72%	—	Moderate	
				5/19/33	62%	40%	Slight	
156	48	M	Visceral syphilis	2/ 1/33	70%	52%	Moderate	Primary lesion in 1914. No antisyphilitic medication. Subtotal thyroidectomy 1924 for exophthalmic goiter. Recurrence at entry. Preoperative Lugolization. Subtotal thyroidectomy. Examination at entry also revealed positive Wassermann, greatly enlarged smooth liver, palpable spleen; postoperative treatment with Lugol's solution produced decrease in size of liver and spleen before second rose bengal.
				4/10/33	64%	42%	Slight	

improved under therapy. Case 128 was of particular interest as a splenectomy was performed and we had an opportunity to study the liver and spleen grossly and microscopically. Antisyphilitic therapy administered before the operation did not reduce the size of the spleen or improve the liver function. Immediately following the splenectomy, the dye retention became greater, but later improved.

II. TREATED GROUP:

A. Those who had received little treatment.

Twenty-two patients received a small amount of antisyphilitic therapy before examination for liver function. In five cases the type of therapy was unknown as it had been given to the patient before entrance to the clinic. In 17 cases arsenicals had not been given; one received mercury and potassium iodide, and the other 16 mainly bismuth. Only one patient of this group showed an abnormal retention of the dye, and his record is listed in table 3. The treatment he received before entering the clinic consisted of two months of mercury rubs in 1924, and 20 intramuscular injections in 1930. Because of lack of clinical improvement on bismuth, the arsphenamines were tried cautiously, and the combination of drugs produced improvement in rose bengal excretion, but no clinical change.

Two patients (53 and 109) received arsenic only in the form of tryparsamide. The former had been given 35 grams of tryparsamide and 26 injections of bismuth before the first rose bengal test which was slightly abnormal. This was followed by 14 injections of mercury salicylate, 10 of bismuth, and 40 grams of tryparsamide. The next test showed practically no change. It is quite probable that in this case the impaired liver function was not produced by the tryparsamide, for its continued use did no further harm. The second patient was examined long after a small amount of tryparsamide had been given and showed a normal function.

B. Normal liver function—usual antisyphilitic treatment.

This group consists of 76 patients who received either arsphenamine or neoarsphenamine, and showed a normal rate of elimination of rose bengal. Table 4 lists the number of cases and the amount in grams of the arsphenamines given. It is evident that a large amount of these arsenicals can be tolerated by some individuals without interfering with liver function.

TABLE IV

Treated Group; Normal Liver Function

Amount of arsphenamines	2–4 gm.	4–6 gm.	6–8 gm.	8–10 gm.	10–12 gm.	12–14 gm.
No. of cases	6	15	8	9	10	2
Amount of arsphenamines	14–16 gm.	16–18 gm.	18–20 gm.	20–22 gm.	22–24 gm.	
No. of cases	9	5	1	2	1	
Amount of arsphenamines	24–26 gm.	32–34 gm.	44–46 gm.			
No. of cases	1	1	1			

Total: 76 cases

Average: 9.5 grams of the arsphenamines per patient.

TABLE III

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
19	48	M	Cardiovascular syphilis	5/29/31 12/ 2/32 2/ 3/33	84% 80% 64%	58% 60% 44%	Marked Marked Moderate	*Examination:* Liver and spleen not palpable. Treatment before entry consisted of mercury rubs in 1924, and 20 injections of bismuth in 1930. Treatment after 5/29/31 consisted of 6.5 gm. of neoarsphenamine, 44 injections of bismuth, and potassium iodide. After 12/2/32 received 5 injections of bismuth.

TABLE V

Treated Group; Abnormal Liver Function; Never Jaundiced

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
5	60	M	Visceral syphilis	3/ 2/32	80%	60%	Marked	Initial lesion in 1912 treated with mercury by mouth and as rubs. For 10 years up to a year before entry treated with 60 arsphenamine injections and 20 neoarsphenamine injections. Liver and spleen palpable at entry. Between 9/11/32 and 3/3/33 given 4.3 gm. of neoarsphenamine.
				3/23/32	76%	50%	Moderate	
				8/23/32	65%	47%	Moderate	
				9/11/32	64%	—	Moderate	
				3/ 3/33	75%	57%	Marked	
16	48	F	Central nervous system syphilis	7/ 8/31	75%	50%	Moderate	Positive blood Wassermann and spinal fluid Wassermann 1931. Gastric crises. Treated with neoarsphenamine 3.75 gm. and 12 bismuth injections. Died March 1932; perforated peptic ulcer.
				7/24/31	71%	41%	Moderate	
23	38	M	Latent syphilis	3/23/32	60%	40%	Slight	Positive blood Wassermann in 1919. Treated with 12.3 gm. arsphenamine, 4.5 gm. neoarsphenamine, 4.7 gm. mercury salicylate and mercury rubs up to 1923. Left clinic and returned in 1932; no treatment in the interval.
				1/20/33	80%	55%	Marked	
27	50	F	Latent syphilis	3/ 9/32	63%	37%	Slight	No history of infection. Routine examination revealed positive Wassermann and palpable liver. Treated with 36 injections of bismuth and 5.3 gm. of neoarsphenamine before 3/9/32. 12 more bismuth injections before 12/14/32. One injection of neoarsphenamine, 0.3 gm., before 2/10/33. No reaction.
				12/14/32	63%	42%	Slight	
				2/10/33	65%	43%	Slight	
48	38	M	Secondary syphilis	11/18/31	82%	46%	Moderate	Entered with secondary lesions, treated with 7.0 gm. of neoarsphenamine and 12 bismuth injections before 11/18/31. Examination negative. Left clinic.
74	50	M	Central nervous system syphilis	9/ 9/31	75%	50%	Moderate	Treatment consisted of 5.05 gm. neoarsphenamine and 11 ininjections of bismuth before 9/9/31. Followed by 12 injections of mercury salicylate and 1.55 gm. of neoarsphenamine before 12/24/32. No reactions.
				12/24/32	80%	50%	Marked	

TABLE V—*Continued*

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
99	51	F	Visceral syphilis	4/29/32 3/ 3/33	60% 70%	40% 40%	Slight Moderate	Positive Wassermann eight years ago, treated with 2.2 gm. arsphenamine. Palpable liver and spleen at entry. Treated with 12 intramuscular injections of mercury salicylate and then 2.05 gm. of neoarsphenamine. Slight clinical improvement. Liver and spleen not palpable on 3/3/33.
110	54	M	Latent syphilis	9/13/32	62%	44%	Slight	Treatment consisted of 43 gm. of neoarsphenamine and mercury rubs before entry. Liver palpable and extends 3 cm. below costal borger. Present therapy is bismuth.
121	37	F	Latent syphilis	10/ 4/32	62%	40%	Slight	Two years of intensive treatment several years before entry, and 24 injections of bismuth and 10.5 gm. of neoarsphenamine just previous to entry.
131	52	M	Central nervous system syphilis	10/28/32 11/25/32	67% 62%	40% 40%	Slight Slight	Total treatment up to 10/28/32 was 9.2 gm. of neoarsphenamine and 47 injections of bismuth.
136	54	M	Central nervous system syphilis	12/24/32	68%	42%	Slight	Treatment before entry consisted of three injections of salvarsan 11 years ago followed by bismuth, mercury and potassium iodide at intervals. Examination at entry reveals a palpably enlarged liver.
145	27	M	Secondary syphilis	10/25/31 2/24/32 5/18/32 6/26/32	76% 64% 64% 65%	70% 35% 35% —	Marked Slight Slight Slight	Entered with lesions of secondary syphilis on 5/18/31. Treatment with 4.8 gm. neoarsphenamine and 12 injections of bismuth up to 10/25/31. Followed by 3.6 gm. neoarsphenamine and 12 injections of bismuth up to 2/24/32. Then 3.15 gm. of neoarsphenamine up to 6/26/32.
157	49	M	Latent syphilis; diabetes mellitus	2/ 1/33 3/17/33	67% 70%	45% 45%	Moderate Moderate	Chancre in 1902; no treatment until entry. Received 2.7 gm. neoarsphenamine and 10 bismuth injections before 2/1/33. Examination reveals an enlarged palpable liver.

TABLE VI
Treated Group; Jaundice; Recovery of Function

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
14	20	M	Secondary syphilis	2/15/32 1/20/33	75% 55%	40% 33%	Moderate Normal	Onset of jaundice followed second injection of neoarsphenamine. Lasted 4 weeks; cleared by 3/15/32. Subsequent treatment: 32 injections of bismuth and 5.7 gm. of neoarsphenamine without ill effect.
15	37	M	Paresis	12/ 9/31 12/ 9/32	52% 40%	35% 28%	Normal Normal	Chancre in 1923. Intermittent treatment, totalling 12.4 gm. arsphenamine, 14 injections of bismuth and 75 of mercury salicylate up to 1929. Jaundice on 10/8/29 lasting three months. In 1930 treated with 20 injections of bismuth, 20 of mercury salicylate, 26 gm. of tryparsamide, and malarial therapy.
22	49	M	Central nervous system syphilis	11/20/30 1/27/31 3/ 5/31 9/23/31 11/25/32	80% 80% 69% 62% 57%	60% 52% 44% 37% 30%	Marked Marked Moderate Slight Normal	Chancre in 1910. Initial treatment consisted of 15 injections of bismuth started in March 1930. Neoarsphenamine started on 8/5/30. Third injection followed by severe reaction. Onset of jaundice 9/10/30, lasting three months. Liver and spleen never palpable. Since October 1931 has had 34 gm. of tryparsamide.
44	37	M	Latent syphilis	2/15/32	58%	33%	Normal	Chancre in 1915. Treated with mercury and potassium iodide before entry. Given 22 injections of mercury salicylate at entry, then 2.05 gm. of arsphenamine. Jaundice Jan. 1 to 22, 1929. Liver and spleen not palpable. Therapy since then 3.6 gm. arsphenamine, 28 injections of bismuth, 9 of mercury salicylate. Died July 26, 1932 of hypertensive heart disease (no autopsy).

TABLE VI—*Continued*

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
58	25	M	Primary syphilis	11/27/31 2/ 1/32 8/30/32 3/24/33	70% 56% 58% 48%	56% 30% 37% 26%	Moderate Normal Slight Normal	Entered clinic Nov. 1931 with chancre. After 1.8 gm. of neoarsphenamine developed intense jaundice lasting three months. Since then has received 42 injections of bismuth, 13 of mercury salicylate, and 18 of bismarsen without ill effect.
106	18	F	Latent syphilis	5/18/32	56%	28%	Normal	Positive Wassermann in October 1931, treated with four injections each of neoarsphenamine and bismuth, followed by jaundice which had cleared by 3/18/32. Left clinic.
133	51	M	Late syphilis	12/ 9/32 2/17/33	53% 55%	30% —	Normal Normal	Chancre in 1904. Treated with mercury and potassium iodide in 1922, 18 injections of mercury salicylate and 4 gm. of arsphenamine in 1923. Left clinic; no further treatment. Returned in Sept. 1930 with intense jaundice and large palpable liver. Jaundice receded under potassium iodide and mercury by mouth. Started on bismuth in March 1932, followed by 1.8 gm. of neoarsphenamine and then bismuth. Liver decreasing in size.
138	20	F	Secondary syphilis	1/20/33	50%	28%	Normal	Initial treatment consisted of 3.75 gm. of neoarsphenamine. Jaundice followed seventh injection on 10/5/32. Liver palpable, enlarged during jaundice, which lasted two weeks. Treated with bismuth since then.
158	26	F	Latent syphilis	2/10/33 3/31/33 5/25/33	65% — 50%	47% 38% —	Moderate Slight Normal	Positive Wassermann in Nov. 1932. Given 1.8 gm. of neoarsphenamine and two injections of bismuth. Marked reaction and jaundice followed the last injection of neoarsphenamine. Jaundice lasted three months, liver not palpable.

C. Abnormal liver function; no history of jaundice.

An abnormal liver function was found in 26 patients, none of whom gave a history of jaundice. These patients are divided into three classes: (1) those with definitely abnormal retention of the dye; (2) those with slight retention of the dye; and (3) those who were abnormal and later returned to normal. In table 5 are listed 13 cases where the patients showed a marked retention of the dye. Physical examination revealed a large palpable liver in six of these patients, and two of them also had a palpable spleen. Five received injections of arsphenamine after liver function studies had been performed and in three of these (5, 74, and 99) the retention became definitely worse, whereas in one (145) there was improvement, and in the fifth (27) there was but slight change. The 10 cases showing slight retention of the dye are not listed in detail as their exact status is difficult to determine. They will be kept under observation and reported upon at a later time. Three patients had a slightly abnormal retention of the dye at one time, and after further treatment the liver function test showed normal figures. Two of these three patients were tested after reactions to the arsenicals and this may account for the slight abnormality.

D. Abnormal liver function; history of jaundice.

Fifteen patients who had jaundice were studied. In 14 of these the arsphenamines probably played a decisive part in the production of the jaundice. In one case (51) the onset of jaundice was not due to treatment, but the patient is included in this group for convenience. He had received a moderate amount of antisyphilitic treatment before liver function studies were made. The group is divided into three classes. In the first class are nine patients who showed a fairly rapid return to normal function after recovery from the jaundice. Table 6 shows the findings of this class. As was found in our earlier study, the young adult usually makes a complete recovery from the hepatitis and the arsenicals are often well tolerated later. All but one of these patients received less than four grams of the arsenicals before the onset of the jaundice. The next class consists of but two patients (52 and 67) listed in table 7. In the former, the liver function returned to normal after five years; in the latter it is not entirely normal after six years. These two patients probably suffered from a severe degree of liver damage which required a long period of time before the capacity of the liver was restored. The third class, listed in table 8, is made up of three patients who continue to have an abnormal retention of the dye following jaundice. In all three the syphilitic infection was of long standing, a large amount of arsenicals had been given previously, and a history of steady consumption of alcohol was obtained. This combination of factors probably produced some latent damage to the liver, which was followed by a more acute condition. In all three patients the liver was enlarged and palpable; one (95) had a typical cirrhosis, and this is suspected in case 56. The former died following a severe esophageal hemorrhage, and autopsy showed a toxic cirrhosis of the liver. The latter has been followed for three years

TABLE VII

Treated Group; Jaundice; Slow Recovery of Function with Slight Damage

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
52	32	F	Early tabes dorsalis	9/–/28 2/–/30 3/–/31 7/–/32	84% 62% 70% 50%	58% 38% 59% 30%	Marked Slight Moderate Normal	Chancre in 1914. In 1919 treated with mercury and arsenicals. No other treatment until 1927, given 17 injections of mercury salicylate, 10 of bismuth and 3.45 gm. of neoarsphenamine. Jaundice in July 1928. Liver palpable 6 cm. below costal margin at that time. Treated with bismuth mainly since then. Liver not palpable in July 1932.
67	42	M	Latent syphilis	2/2/33	60%	35%	Slight	Chancre in 1919 and in following seven years treated at irregular intervals with arsenicals totalling 18 gm. of arsphenamine. Jaundice in 1927 one year after last treatment. Before entry in 1931 given three injections of neoarsphenamine. Attends clinic irregularly. Liver slightly enlarged.

TABLE VIII
Treated Group; Jaundice; Permanent Liver Damage

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
56	52	M	Late syphilis	11/30	90%	60%	Marked	Initial lesion in 1899; no treatment before entry in 1929. Alcohol taken in excess. Palpable liver at entry. Treatment: 7/29 to 9/29: 1.8 gm. arsphenamine and 22 injections of bismuth. 11/29 to 12/29: 2.4 gm. arsphenamine. 12/20 to 3/30: 14 injections of bismuth. 4/30 to 5/30: 2.1 gm. arsphenamine. 5/30 to 8/30: 12 injections of bismuth. 8/30 to 9/3/30: 1.8 gm. neoarsphenamine. Jaundice after injection on 9/3/30, lasted six weeks. 9/31 to 12/31: 12 injections of bismuth. 8/32 to 12/32: 18 injections of bismuth.
				12/30	83%	59%	Marked	
				1/31	83%	56%	Marked	
				3/31	66%	35%	Slight	
				4/31	71%	40%	Moderate	
				5/31	66%	43%	Slight	
				6/31	92%	76%	Marked	
				8/31	83%	66%	Marked	
				9/31	63%	43%	Slight	
				12/31	55%	37%	Normal	
				3/32	69%	46%	Moderate	
				4/32	62%	37%	Slight	
				7/32	66%	40%	Slight	
				8/32	62%	38%	Slight	
				12/32	73%	45%	Moderate	
75	50	M	Latent syphilis	1/21/31	74%	45%	Moderate	Initial lesion in 1908, no treatment. Positive blood Wassermann in 1929. Treatment consisted of 14 injections of mercury salicylate followed by 3.6 gm. neoarsphenamine in July 1929. Left the clinic until April 1930, when he returned because of marked jaundice which lasted to Sept. 1930. Liver enlarged. Left clinic Nov. 1931.
				4/ 2/31	55%	35%	Normal	
				9/ 7/31	66%	40%	Slight	
95	33	F	Visceral syphilis	4/20/32	88%	80%	Marked	Secondary lesions in 1926, treated intermittently with bismuth and arsenicals. Just before entry received 25 injections of neoarsphenamine followed by jaundice. History of excessive use of alcohol. Examination at entry revealed markedly enlarged liver, slightly enlarged spleen. Treated with potassium iodide and mercury salicylate. Numerous hemorrhages from esophageal varices before death on April 11, 1933 following massive hemorrhage. Autopsy: Pathologic diagnosis: toxic cirrhosis of the liver.
				5/18/32	88%	86%	Marked	
				2/ 9/33	82%	70%	Marked	

and tested frequently. There are periods when the excretion of dye approaches normal and periods when it is markedly delayed. These patients certainly have suffered permanent damage to their liver. Of the first group of nine patients, four have since taken courses of neoarsphenamine, one has had bismarsen, two have had tryparsamide, and one of these has also had malarial therapy. The two remaining patients have been jaundiced at such a recent date that, although they have normal liver function, they have not been treated as yet with the arsphenamines. The first seven patients indicate that when the dye excretion returns to normal the liver may tolerate the arsenicals without toxic effects.

Comment

The findings presented demonstrate that latent hepatic disease is not uncommon in patients under treatment for syphilis. In the entire series of 152 patients, 46 were found to have an abnormal liver function as demonstrated by protracted retention of rose bengal dye in the circulation. Seven of these patients presented other definite clinical evidence pointing toward a pathological process in the liver, and 13 had a history of jaundice. The remainder, or 26, had an impaired liver function which was detected only by the rose bengal test. This latter group may be definitely injured by the injudicious selection of antisyphilitic remedies.

Syphilis of the liver was found in but three patients, those listed in table 2. It was suspected in several others and probably played a part in the hepatic lesions of some, but this could not be proved. Of the three above mentioned cases, patient 19 showed marked improvement under treatment with potassium iodide and bismuth, and with this clinical improvement the retention of dye diminished. The patient listed as case 70 presents a diffuse hepatitis and will probably go on to a chronic state with cirrhosis. In the third case (156) there was improvement under treatment with potassium iodide.

As observed in a previous series of patients,[2] there is a return to normal function after an arsphenamine jaundice in the majority of cases. The age, the amount of arsenicals received, alcohol consumption and the previous state of the liver are some of the factors which determine whether a complete recovery of liver function will occur. The ability of these patients who do recover to be treated again with the arsenicals without producing clinical or laboratory evidence of impaired function strongly suggests that complete healing had taken place. In a certain percentage of cases permanent liver damage occurs and further treatment may be very harmful.

On many occasions an abnormal retention of the dye in conjunction with the history and physical findings has helped us to decide upon the type of antisyphilitic therapy to be instituted or resumed. Following an arsphenamine hepatitis as indicated by jaundice and an impaired liver function, the arsenicals are not administered until the dye excretion has been demonstrated to be normal. Indiscriminate treatment with arsphenamines can do these

patients considerable harm, notwithstanding the fact that in certain types of cases arsenicals should be given as soon as possible. The patient with early syphilis developing jaundice during the first course of arsphenamine is in urgent need of the arsenicals, and with recovery of liver function may again tolerate them.

The treated patients who showed evidence of liver damage received more of the arsenicals than those who showed a normal liver function. However, in this latter group there are many who have also been given large amounts of the arsenicals.

Summary

1. The results of the rose bengal liver function test in 152 patients with syphilis are reported.

2. Latent hepatic disease was demonstrated in 26 patients by means of this test.

3. Large amounts of the arsphenamines may be tolerated without apparent ill effects upon the liver.

4. In the presence of latent hepatic disease the rose bengal liver function test is a valuable aid in the care of the patient with syphilis.

5. In 20 patients with clinical evidence of hepatic dysfunction the findings obtained with the rose bengal liver function test paralleled the clinical picture.

6. Although the majority of patients recover from an arsphenamine hepatitis a small number suffer permanent liver damage.

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THE TREATMENT OF CIRCULATORY FAILURE*

By Louis M. Warfield, A.B., M.D., F.A.C.P., *Milwaukee, Wisconsin*

For years investigators have been trying to unravel the processes which go on in the body following the initial shock of a violent injury, and further what takes place in the body in the condition known as secondary shock. A considerable measure of success has crowned the efforts, until now it is very generally agreed that not toxemia[1] but blood volume changes due to loss of fluid in the injured part play the chief rôle. With this concentration of blood there is also hypochloremia, low venous pressure, insufficient venous return flow to the heart and therefore rapid heart action and apparent circulatory failure. The practical application of the knowledge gained by the physiologists has lagged far behind. A great inertia takes hold of those who write textbooks so that it is often many years before radical changes, in methods of therapy particularly, become an integral part of the sections on treatment.

It would carry us too far to go into the details of the newer physiology of muscle contraction[2]; suffice it to emphasize that an adequate supply of three substances is essential for all muscle work—glucose, insulin, and oxygen.[3] The heart muscle is no different from the skeletal muscles in its dependence upon these three substances. It differs fundamentally in several particulars. First, it is made up of cells which have no membrane around them comparable to the sarcolemma in skeletal muscle. Second, the nerve supply, so far as known, has no end-plates but is motivated by specialized nerve tissue. Third, a stimulus applied to the heart produces maximum contraction, however slight the stimulus may be. Fourth, the heart muscle is much less tolerant of oxygen debt than skeletal muscle and it is more sensitive to accumulation of lactic acid. It is like the skeletal muscles in that the strength of the contraction is dependent upon the initial length of the fibers, and also in that up to certain limits the more the fiber is stretched the stronger the contraction (Starling's law). In normal heart muscle it appears impossible to do permanent harm by any load placed upon it. The factors of safety in the body, particularly the vital capacity of the lungs and the sensitivity of the respiratory center to decreased pH of the blood,[4] cause the whole body to stop before the heart muscle is damaged.

The adequate stimulus to ventricular contraction is diastolic filling which is dependent upon venous return flow. The normal state of the circulation depends upon the condition of the peripheral vessels (vasomotor tone) as well as upon the heart. There are further imponderable factors in the body which von Bergmann calls "humoral" and Fr. Kraus calls "protoplasm dynamics" which play a part in cardiovascular decompensation as well as the factor of oxygen exchange in the tissues themselves. No amount of extra

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work so far as known causes the normal heart to hypertrophy, and the cardiac glycogen can not be reduced by any demand put upon it provided there is an adequate supply of oxygen.[2] The reserve is so great that, provided adequate supplies of oxygen, glucose and insulin are furnished, it performs extra work without becoming measurably hypertrophied. It is otherwise if the muscle is overstretched or damaged by some previous bacterial infection, or if the circulation in the coronary arteries is diminished while the muscle is being loaded. Eyster[5] has shown that sudden overstretching of the normal heart of a dog by any method which rapidly increases diastolic volume will cause hypertrophy when the animal is immediately exercised to the point of exhaustion before time for compensation adjustment is given.

So far as our present knowledge goes acute dilatation of the heart is the result of anoxemia[6] (this is contrary to the statement in most textbooks) or of excessive load on an already damaged heart. Acute dilatation does not occur in febrile infections when the heart was previously undamaged, except in the antemortem state when anoxemia supervenes.

For convenience, circulatory failure may be divided into (a) central and (b) peripheral; but no clear cut distinction can be made, and as a matter of fact the whole cardiovascular system is a unit and cannot be separated too sharply into its two chief parts. Yet, as a matter of clinical as well as experimental knowledge, one or the other part usually fails first. It is then often possible at the bedside to evaluate the more important feature of the failing circulation. No intelligent treatment can be administered unless there is understanding of the factors which produce, on the one hand central or heart failure, on the other hand peripheral failure.

It is well known that all the blood in the body is not in active circulation under conditions of ordinary life.[7] What Krogh demonstrated for muscle and Richards for kidney glomeruli is true for the body as a whole. The value of 75 to 85 c.c. of blood per kilogram of body weight as the blood volume of a resting, fasting, recumbent person represents only the "effective" volume. How much blood is stagnant or very sluggishly circulating in the various depots of the body is a matter of pure guess. Since Barcroft described the spleen of the dog as the important depot in that animal, whence a considerable amount of blood could be rapidly thrown into circulation, increasing attention has been paid to the storage areas in the human body. Eppinger[8] conclusively proved that in man the spleen was of no importance as a depot. Wollheim[9] has shown that the subpapillary capillary plexus of vessels in the skin is probably the most important depot under ordinary conditions. The splanchnic area has long been known to be a huge bed capable of containing a large part of the blood. These are the two most important depots. The liver is to be considered also as well as the lungs under certain pathological conditions.

The subject of heart failure would seem to be rather a trite one except for the fact that new concepts are being established which possibly give us a little better understanding of the condition and a basis for more rational

methods of treatment. Within the past few years, in 1928, Wollheim,[10, 11] as the result of work in von Bergmann's clinic, divided cardiac decompensation into two groups which he called plus and minus decompensation. His reason for this division is that he found in certain cases that the blood volume was definitely increased, while in other cases it was definitely decreased. Eppinger and Schürmeyer,[8] using the CO method of estimating blood volume, showed that hypertonics have already in circulation a larger blood volume than normal and this is not increased much by exercise or the application of heat, in contrast to the man with normal pressure whose blood volume under such conditions increases 15 to 20 per cent.

The chronic plus decompensation cases, which are the most common, are those whose breakdown is the result of excessive strain such as occurs in hypertonia, in aortic insufficiency, and in most cases of mitral stenosis especially when combined with insufficiency and a large left ventricle.

The chronic minus decompensation cases are seen in primary disturbances in oxygen exchange in the lungs, in pulmonary stenosis, pulmonary sclerosis, not infrequently in mitral stenosis, in emphysema, and in thyrotoxicosis. In the acute form they are seen in lobar pneumonia, in the bronchopneumonia of grippe, in toxic infectious diseases and in circulatory shock. The blood volume may be as low as 40 to 50 c.c. per kilogram of body weight.

The plus cases are characterized by dyspnea, orthopnea, edema, distention of the veins in the neck, and cyanosis, especially of the lips and acral parts. Pressure of the liver, as Plesch showed, increases the distention of the veins on the right side of the neck. These patients are more comfortable when sitting up with the legs hanging down as the blood volume is then reduced from 400 to 1000 c.c. (Wollheim), by the filling of the subpapillary skin plexuses of the legs.

The most striking characteristic of the chronic minus cases is the absence of dyspnea when at rest. These patients are comfortable lying flat in bed. There is no distention of the neck veins. Cyanosis is found in patches in the skin. The blood pressure is not much, if any, decreased below the normal figure in compensation because the arterioles still retain their tone. It may even be higher than in the compensated state.

Such cases are considered to be instances of vascular insufficiency with blood held back in the depots, in contradistinction to cardiac insufficiency where more blood is actually in circulation.

As most of the cases of central cardiac failure which are seen in patients are those of plus decompensation, the treatment is that well recognized for such cases, namely: digitalis in adequate dosage, strophanthin (ouaibain) in certain emergency cases, venesection, diuretics, carbohydrate diet limited in amount. Under certain conditions the oxygen tent or oxygen chamber is of great value. Wiener[12] has recently called attention to the value of small doses of insulin followed by intravenous glucose, 50 to 200 gm., in the treatment of these cases. It is known that glucose is used up in heart muscle in

direct proportion to work done. It has also been shown that there is increased lactic acid in the blood in these failing hearts [3, 13] and it is known that the heart muscle is quickly poisoned by a very slight excess of lactic acid. The sluggish coronary circulation leads to anoxemia and thus to the consequent dilatation with further decrease in stroke and minute volume. The administration of oxygen, glucose and insulin is logical treatment and has a sound experimental basis.

The treatment of the minus decompensation cases, those characterized by lessened blood volume, presents an entirely different problem. While Wollheim is probably correct in dividing the cases as he does on the basis of much careful work, yet one must bear in mind that a sharp distinction cannot always be drawn between cardiac and vascular insufficiency. There is, for example, minus decompensation in infarct of the heart, in subacute bacterial endocarditis, often in recurrent rheumatic endocarditis and in malignant endocarditis. These are cases of cardiac failure where there is definite damage to the heart, yet the blood volume is low. The collapse is not peripheral but cardiac. The venous pressure is low. As digitalis decreases blood volume even in normal persons [11] and further reduces venous pressure it obviously would be contraindicated.

There are cases, however, of chronic minus decompensation seen chiefly in the cardiovascular breakdown of thyrotoxicosis where patients are not usually dyspneic, where venous pressure is not high, where there is no cyanosis or the cyanosis is distributed in patchy areas over the skin. In spite of the fact that the arrhythmia present is practically always auricular fibrillation, experience has shown that digitalis has but little effect upon the symptoms and signs. Subtotal thyroidectomy, preceded by iodine administered in some form, is the most successful treatment known at the present time for this type of cardiac failure.

I wish to direct particular attention to the treatment of the cases of so-called heart weakness which often comes on in the course of most of the infectious fevers when the patients are seriously ill. But before discussing the treatment some reason must be given for the rather unusual conclusions which will be drawn.

If one looks in the recent textbooks of medicine or therapeutics under the sections on treatment of the various infectious fevers, he will find the statement that the heart fails and that the heart should be stimulated. Practically all advise digitalis in some form, some extolling it as the ideal heart stimulant (Beckman), others saying that some give it prophylactically at the onset of fever, especially in pneumonia and that some do not (Musser). Nowhere does one find any other idea expressed but that the heart fails.

Now let us examine these two, one might almost call them axioms in the light of modern physiological knowledge. First, as to the statement that digitalis is a valuable heart stimulant it may be said that all the information we now possess is that digitalis is not a heart stimulant. Its action is primarily upon the vagus nerves and upon the junctional tissues. Further it

reduces blood volume and may have some dilating action on the coronary arteries, but that is doubted.[14] True, in toxic doses it causes the heart to go into tetanic contraction due probably to the direct action of digitoxin upon the muscle. Holzbach[15] states that it is senseless to give digitalis for the purpose of protecting the heart. Randolph[16] has criticized the routine treatment of pneumonia with digitalis, stating his belief that it is ineffective and indeed not infrequently injurious. Christian[17] believes that digitalis does have some tonic action upon large hearts, tending to protect them from further dilatation. In this sense it may be called a heart stimulant but the hypertrophied heart is not the heart in a patient with serious infection.

The next belief is that the heart fails in cases of serious infection. But does the heart fail as the initial circulatory symptom? Holzbach, Randolph, Wollheim, von Bergmann, Romberg and Passler, and many others say emphatically that the heart itself does not primarily fail in such diseases. It has been found in cases of secondary collapse in peritonitis that several conditions develop: (1) there is low blood volume due to loss of fluid into the tissues; (2) there is concentration of the blood; (3) there is loss of chlorides in the blood; and (4) there is low venous pressure. It is known that the heart has an enormous reserve force, that given oxygen, glucose, and insulin it is practically impossible to wear it down. It is known that stimulus to contraction comes from adequate diastolic filling. It is known that a certain head of pressure must be maintained in the coronary arteries in order that the organ may do its work. The deleterious effects of dehydration and of disturbed mineral balance are beginning to be appreciated. In fevers when the heart apparently fails the four conditions cited above are all present.[18] It would therefore seem that the so-called heart failure is quite comparable to the condition described as secondary shock. It has nothing to do with the heart primarily but the effect upon the heart is necessarily profound. The decreased blood volume leads to decreased venous return flow so that the heart is not dilated but is smaller than normal. The vasoconstrictor center in the medulla is stimulated so that the arterioles contract while the capillaries dilate due to the histamine-like substances produced by breaking down of the proteins by the bacterial toxins. In this stage the blood pressure is not materially changed, as I have repeatedly found. The venous pressure is probably low. However, the low blood volume and insufficient venous return flow cause the heart to beat faster in order to keep the minute volume sufficient to carry on the circulation. If the circulatory failure is greater the blood volume becomes less, the heart beats faster, the pulse becomes smaller, and the blood pressure falls. A point is reached when there is not diastolic pressure sufficient to keep circulation in the coronary arteries. Anoxemia of the muscle results, lactic acid is not carried away, it poisons the heart, and the muscle dilates. At autopsy the pathologist finds a dilated right heart and concludes that dilatation of the heart was a factor in the death. It is true, but that is a condition brought about very shortly before death.

The actual effects of the decrease in blood chlorides is not definitely known. It probably has to do with disturbances in acid-base equilibrium and would suggest alkalosis, yet determinations of the alkaline reserve in pneumonia have not shown any consistent changes from the normal. The blood chlorides appear to be necessary for phagocytosis. Fleming[19] has shown that very slight increase, as little as 0.01 per cent, greatly stimulates phagocytosis.

Consider what usually happens when a person acquires some serious infection. Previously in good health, within a few days or a week or two his heart apparently wears out. In the light of what we know of the heart this seems quite incomprehensible. What we can understand is that as a result of the toxic products of bacteria the proteins of the tissues are broken down resulting in an increased osmotic pressure which draws fluid from the capillaries thus reducing blood volume.[20] In the infectious fevers some such process as the following probably takes place. "As the provocative poison reaches the tissues (perhaps the muscles in particular) catabolic changes are initiated which increase the affinity of the tissues for water. This general demand upon the blood for water tends to reduce the blood volume, especially at the expense of the surface blood. The skin immediately becomes cooler, and this arouses the nervous regulation against cold, thus exaggerating the processes of vasoconstriction and hemo-concentration. This continues until the blood becomes warm enough for the nervous centers to interpret the temperature as comfortable or neutral." (Barbour.) With reduced circulating blood volume and concentration of the blood, diastolic filling is profoundly disturbed. The heart speeds up its rate; its nutrition suffers. The peripheral circulation then is the source of the initial circulatory failure which most people until recently have ascribed to the heart.

Emphasis must be placed on the idea that the heart does not fail. Romberg and Passler[21] years ago showed that even in most severe experimental infections in rabbits the functional capacity of the heart does not suffer. If the conditions listed above which bring about the so-called heart failure could be brought back to normal, the heart would be found to be carrying on as usual. Recovery from disease means the return to normal blood volume, normal chlorides, normal concentration of blood, normal venous pressure.

Treatment

More than 20 years ago when typhoid fever was so prevalent, I thought that by using gravity to assist in venous return I might combat what appeared to be circulatory collapse. Hence when the pulse began to be increased I elevated the foot of the bed about 10 inches. That often proved sufficient treatment. If the circulatory failure became greater, the patients' legs were bandaged from the ankles to the hips. I knew nothing of measurements of blood volume then, but recent studies by Wollheim[11] show that these procedures increase circulating blood volume. Fluids were pushed, high carbohydrate diet given, and every effort made to keep the patient from

losing weight. Those days are over but there are other serious infections to be treated and the problem in such cases is still how to treat the failing circulation in the most rational way.

No experimentation is more difficult than that in the clinic on human subjects. Control cases exactly similar to those treated in any special manner are not possible to secure. By the omission of the special treatment in alternate cases an approximate control series can be obtained, but such alternate cases are not true experimental controls. Further, the human being is so constructed that one gets well in spite of what is done, another dies in spite of what is done. Yet there should be principles of proper treatment and it is to these principles that we now turn.

What have we to do, and what means have we with which to do what should be done?

Obviously circulating blood volume should be increased and the chloride content of the blood should be raised. To achieve these results we have certain drugs and the use of fluids by intravenous administration. As digitalis decreases blood volume its use is absolutely contraindicated except in cases where auricular fibrillation exists. The so-called vasomotor drugs increase the circulating blood volume. Into this class fall camphor and its substitute preparations, Cardiozal and Hexaton, and likewise caffein, strychnine and Ephetonine. Graphic results of experiments in the clinic are published by Wollheim.[10] The most useful drug in my hands has been strychnine sulphate. It is said to increase blood volume (Wollheim). It should be given in large doses hypodermically (gr. 1/15 to 1/10 to an adult every hour or two). This may seem heroic and not devoid of danger. Yet I have given gr. 1/10 hypo. every hour for 36 hours; there was no evidence of strychnine poisoning, and the patient, desperately ill with typhoid fever, recovered. The strychnine may have had no part in her recovery. Caffein-sodium benzoate and camphor preparations such as Metrazol are said to increase blood volume but also are said to stimulate the vasoconstrictor center in the medulla. These drugs were highly extolled before it was known that in circulatory collapse the center is in a state of increased tone. Personally I have not used these drugs for some time. Adrenalin, ephedrin and pituitrin are recommended. In sudden collapse I have used both adrenalin and pituitrin with apparently good result. The action of both is transient, especially adrenalin. Pituitrin (pitressin) is said to have a too violent constrictor effect. Adrenalin may be given in the fluid of intravenous transfusion with saline or glucose or the combination of the two.[22] This prolongs its action and simulates in some degree natural processes.

The most logical and satisfactory method of increasing blood volume is by introducing fluids intravenously. Normal saline with glucose (dextrose) is always on hand. "Dextrose, intravenously given, resembles the antipyretics in that it reduces the temperature in fever, causing the blood to become more dilute than under normal conditions. This supports the contention that blood sugar plays a rôle in antipyretic action."[20] It should be

given in large quantities, three to four liters or more in 24 hours. A resting, fasting person loses about three liters of fluid daily. We live in water. The consequences of even mild dehydration are serious. Many use glucose and saline but are content with a liter a day. I would urge larger quantities for obvious reasons. But saline-glucose has a decided drawback. The fluid does not remain in the blood for long but is drawn out into the tissues. The effect is not lasting. What is wanted is a fluid which contains colloids which will not only remain in the vessels but which may withdraw fluid from the tissues into the vessels. Naturally the ideal fluid is blood itself or blood plasma. Blood has been used repeatedly but the reasons usually given for its good effects included the supposed action of antibodies. The real reasons are that it not only increases and maintains blood volume, introduces important ions such as Ca, Na, K, but it adds oxygen carrying red blood cells. This last is not so important if there is no anemia. Lastly, it has been shown that acacia solutions also have the property of maintaining blood volume. Barbour and Baretz found that acacia similarly tends to dilute the blood in fever and to reduce the temperature, which it does not do in normal animals. Now there is available acacia solution which can readily be diluted to the proper 6 per cent by the addition of distilled water. This also has chlorides in solution. Not enough experience has accumulated so that we know how much or how often acacia solutions should be given. Practically it would seem that the amount could be controlled by hematocrit readings. These have now been simplified so that any laboratory should be able to perform them. This is a clinical problem which must be worked out. Since ill patients have recovered without these transfusions it would be sensible to err on the safe side and give not more than 500 c.c. of blood (citrated or whole) or 500 c.c. of 6 per cent acacia solution every three to four days. In the meantime one should give daily intravenous transfusions of glucose and saline in large amounts and very slowly to reduce the possibility of "speed shock."

Summary and Conclusions

Cases of circulatory failure may be classified into two groups: (1) central, and (2) peripheral. The former is usually accompanied by increased blood volume, the latter by decreased blood volume. This does not hold true where the heart muscle is acutely damaged as it is in coronary occlusion or in purulent embolism of the smaller coronary arteries or in acute rheumatic heart conditions.

The first group, called plus decompensation, is characterized by dyspnea, orthopnea, cyanosis of lips and acral parts, and increased venous pressure. The second group, called minus decompensation, has low blood volume, no dyspnea on lying down, patchy skin cyanosis, and low venous pressure. This last group includes fewer chronic cases than does the first group. The circulatory failure of thyrotoxicosis is the most commonly seen chronic form of minus decompensation. These two groups can usually be recognized at the bedside.

The acute cases of minus decompensation correspond to circulatory failure in all the severe infections. It is peripheral circulatory failure, not failure of the heart itself, and in this failure the following four conditions are found: (1) decreased blood volume and insufficient venous return flow; (2) hemoconcentration; (3) decreased blood chlorides; and (4) low venous pressure. Arguments are advanced to prove that this condition is that of so-called secondary shock.

Since this is true, it follows that the heart itself does not fail in infections until just before death. The measures which are very widely used to stimulate the heart in infections must be futile: first, because the heart is not functionally impaired even in severe infections; second, because we know of no real heart stimulant even if we desired to stimulate the heart itself.

The treatment of the plus decompensation cases is that commonly employed for cardiac decompensation.

The treatment of the minus decompensation cases should be directed toward correcting the four conditions listed above. In certain cases the head-down position and crowding fluids by mouth will suffice. In general, saline solution and 10 per cent glucose should be given intravenously (very slowly to avoid "speed shock"), in amounts up to 3 to 4 liters or more daily. Also one can use transfusions of whole or citrated blood or 6 per cent acacia solution. Probably these transfusions should not be used in amounts greater than 500 c.c. and at 3 to 4 day intervals.

Drugs to be recommended are those which increase blood volume. These are strychnine in adequate doses, caffein sodiobenzoate, Metrozal, adrenalin and pitressin. Adrenalin may be added to the saline-glucose transfusion.

Digitalis is considered to be contraindicated chiefly because it decreases blood volume.

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SPOROTRICHOSIS

REPORT OF A CASE ORIGINATING IN NEW YORK *

By George M. Lewis, M.D., and J. Homer Cudmore, M.D., F.A.C.P.,
New York, N. Y.

In a recent publication, Hopkins and Benham [1] reviewed the incidence of sporotrichosis in New York State, and found that only one culturally proved case had been reported previous to their communication. The first case was presented by Howard Fox [2] before the New York Academy of Medicine in 1921. The patient was a sailor and probably acquired the disease in the tropics. The two cases reported by Hopkins and Benham [1] included one observed by Osborne in Buffalo in 1928, and one studied by them in New York City in 1929. The second case probably developed the infection in Monticello, New York. Cases having clinical evidence in favor of the diagnosis of sporotrichosis were reported by Turrell,[3] Lapowsky,[4] Wise [5] (in whose case the symptoms were typical) and Walzer.[6] Mount's [7] report of an unusual type of sporotrichosis, although of great interest, was unfortunately deficient in laboratory confirmation.

Clinical Types of Sporotrichosis

1. *Localized Lymphangitic.* Most of the reported cases in the United States fall into this group in which a primary lesion or chancre appears on an exposed part of the body. This lesion is indurated; softening and abscess formation may take place; an indolent ulcer may develop or it may vegetate. Rarely the disease remains localized to this single lesion. Usually, after a week or more, a painless ascending inflammation develops in the regional lymphatics along the course of which secondary nodules form and undergo similar changes to those noted in the chancre. Regional lymph node enlargement is uncommon (an important diagnostic point in the clinical differentiation from tularemia, in which latter disease lymph node enlargement is a constant finding). Systemic symptoms or involvement are uncommon. There is little if any tendency to spontaneous recovery. Scarring of varying degrees of severity remains when the lesions involute.

2. *Disseminated Subcutaneous.* In this variety, commonly observed in France, small, hard, painless, subcutaneous nodules of varying number appear in scattered locations over the body. Within three to six weeks, the skin becomes involved, the central part of the nodule softens and forms an abscess which may discharge if traumatized, forming a cup-shaped ulcer with a firm indurated border. New lesions may continue to appear indefinitely in the untreated patient.

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From the Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital, Columbia University, Dr. George M. MacKee, Director; and the Manhattan General Hospital.

3. *Disseminated Ulcerating.* Although similar to the preceding type, this form is distinguished by a tendency to early spontaneous ulceration of the lesions. The ulcerations vary in size and character a great deal. At times large crateriform ulcers develop simulating tuberculosis or tertiary syphilis. There is little if any tendency to spontaneous cure. In the untreated patient the general health may become impaired, with the appearance of symptoms of toxemia.

4. *Epidermic.* The primary lesion in sporotrichosis is practically always subcutaneous. In some instances the epidermis at adjacent or remote sites becomes secondarily infected, papules, pustules and small ulcers developing. Rare cases have been described in which the disease is limited to the skin, and in such instances tuberculosis is differentiated with difficulty. The mucous membranes may also become secondarily infected in cases of the disseminated or ulcerating varieties. The organism is said to be capable of remaining as a saprophyte in the mouth or other mucous surfaces after the disease is apparently eradicated, rendering the patient a possible "carrier."

5. *Systemic.* At times the sporotrichium invades the deeper tissues and organs. In the majority of instances this occurs in the disseminated varieties when treatment is not promptly instituted. The differential diagnosis must exclude cancer, syphilis, tuberculosis and other infections as the etiological factor. The bones or joints may be affected, the tibia being the most common site of the infection. Invasion of the muscles and glandular structures may occur and a number of instances of pulmonary involvement have been reported. Although a common site of involvement in laboratory animals, the epididymis is rarely affected in humans. Gastrointestinal and cerebrospinal involvement is said to be extremely uncommon.

In the following report, which we believe describes the fourth culturally proved case of sporotrichosis originating in New York State, the patient had not been out of New York City for many months prior to the onset of the disease.

Case Report

History. Miss E. H., aged 34, single, an office worker, was first seen on January 27, 1933. There were six granulomatous lesions on her right arm. The first lesion appeared four months previously on the extensor surface of the forearm (figure 1) as a small reddened point of indefinite nature, gradually increased in size, became pustular and finally formed a subcutaneous abscess. Within a month the five other lesions progressively appeared along the arm, the last one approaching the axilla. (Figure 2.) The patient had not handled raw fruit, vegetables, or flowers, nor had she come in contact with animals. She had worked in the garden a few days previously, transplanting some cactus plants. While there, she wore rubber gloves. The initial lesion was above the skin covered by the gloves but she was unable to recall any scratch or abrasion. The lesions were all incised with the exception of the last one. Despite the good drainage so established and the continuous use of wet dressings and antiseptic washes, healing did not take place. The lesions were not painful.

Examination. The patient was well nourished, being about five feet six inches tall and weighing 160 pounds. The temperature was normal and the pulse rate was

72. She appeared to be in vigorous health. On the right arm were six cutaneous and subcutaneous well-defined tumefactions (figures 1 and 2), the largest being the initial lesion. This was situated on the extensor surface of the forearm, three inches above the wrist. The lesion was irregular in outline, of a dusky red appearance at the periphery and exhibited an ulceration in the mid portion. Thick ropy pus covered the ulcer and could be expressed from two sinus tracts present in the outer part of the lesion. Exuberant granulation tissue was visible at the base and bleeding was readily produced when this tissue was but lightly touched. On palpation, the mass was firm

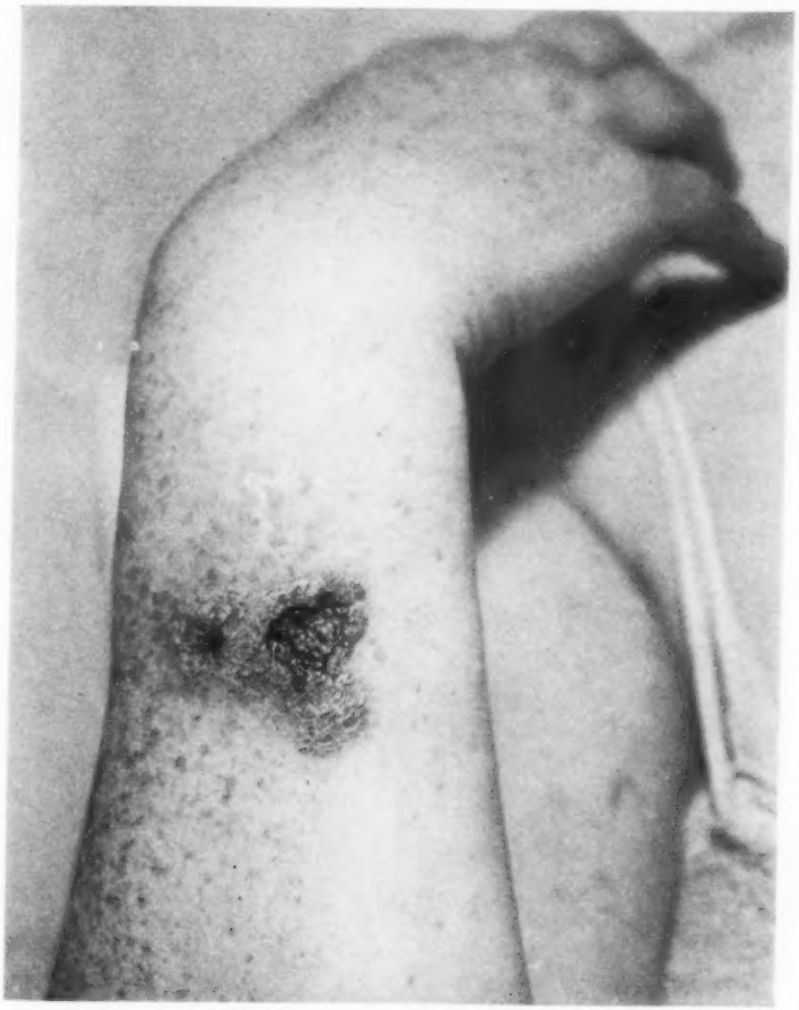

FIG. 1. Sporotrichotic chancre.

but not cartilaginous and was freely movable. The remaining five lesions were smaller, were soft on palpation and had central openings from which thick, yellowish-white pus exuded; they were more superficial than the primary one. No pain or tenderness was noted upon manipulation. The masses were joined by a well defined and distinct lymphangitis but there were no palpable lymph nodes.

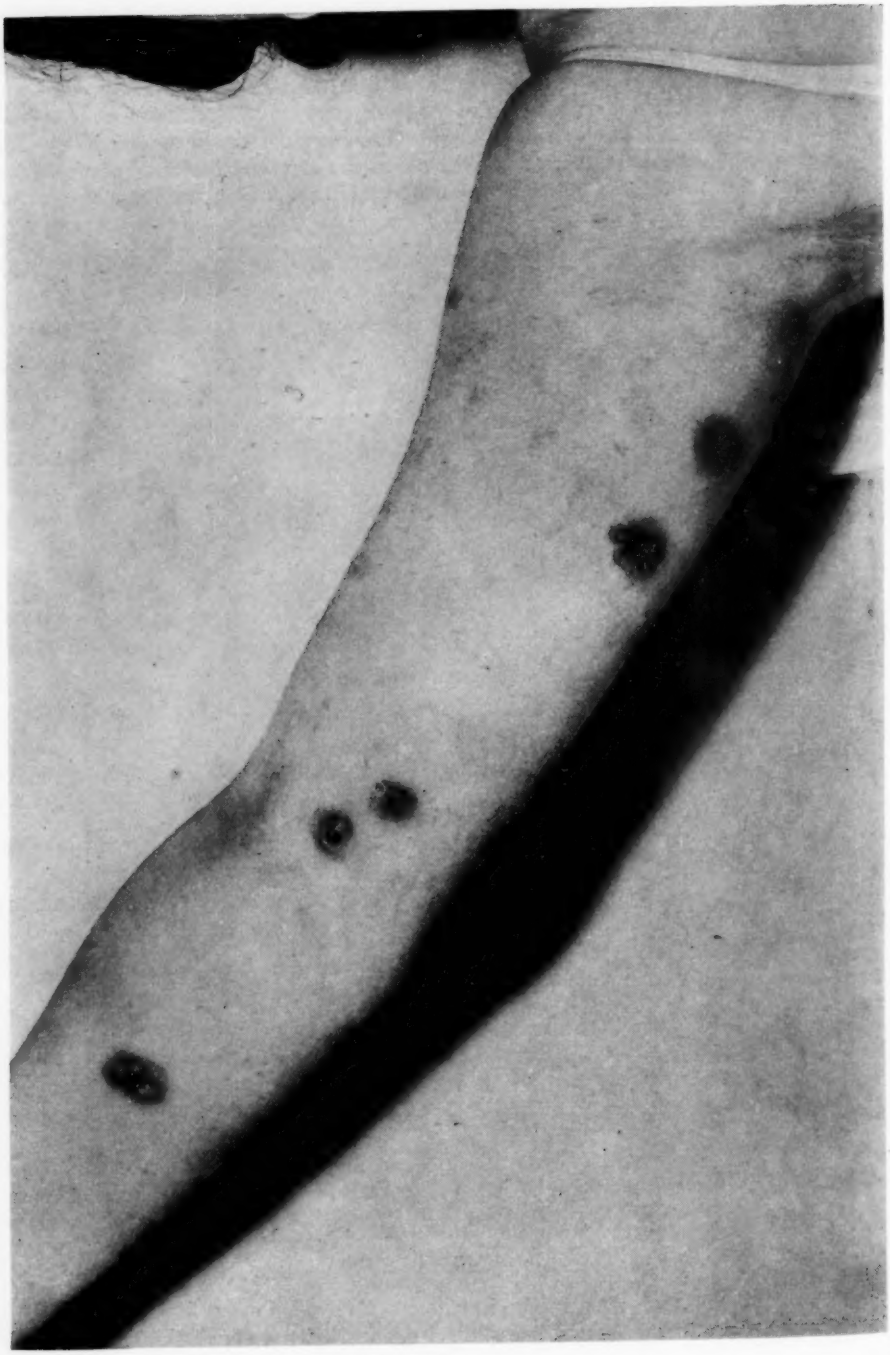

FIG. 2. Secondary sporotrichosis lesions.

Cultural Findings. No fungi were found upon direct examination of secretion despite numerous attempts. At a later date, when the patient was under treatment, the process was repeated, using the technic advised by Lawless,[8] but without success. On culture, at room temperature, using Sabouraud's glucose media, fungus colonies

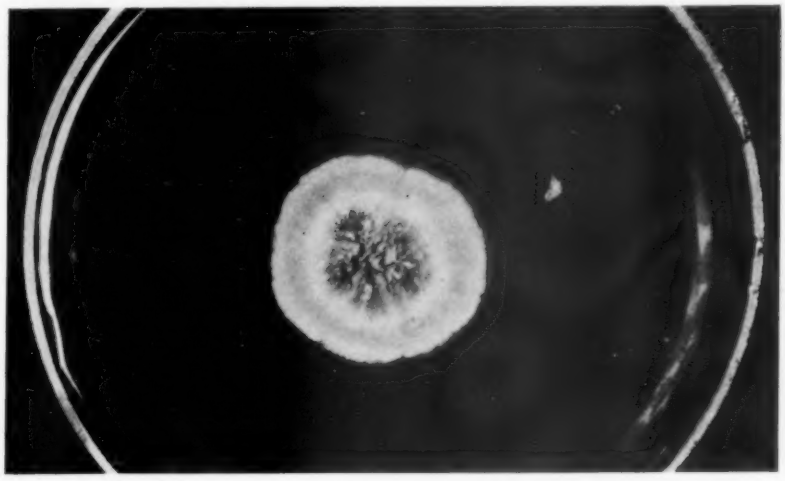

FIG. 3. Colony of *Sporotrichium schenkii*, two weeks old.

developed in 19 out of 20 tubes inoculated with pus. There was practically no bacterial or mold contamination. Growth was noticed on the seventh day after inoculation as a moist, pin-point sized area with a fine fringe. The area slowly increased in size and in two weeks was 2.5 cm. in diameter, was of light brown color and the surface was moist and convoluted. Pigment developed slowly and the growth gradu-

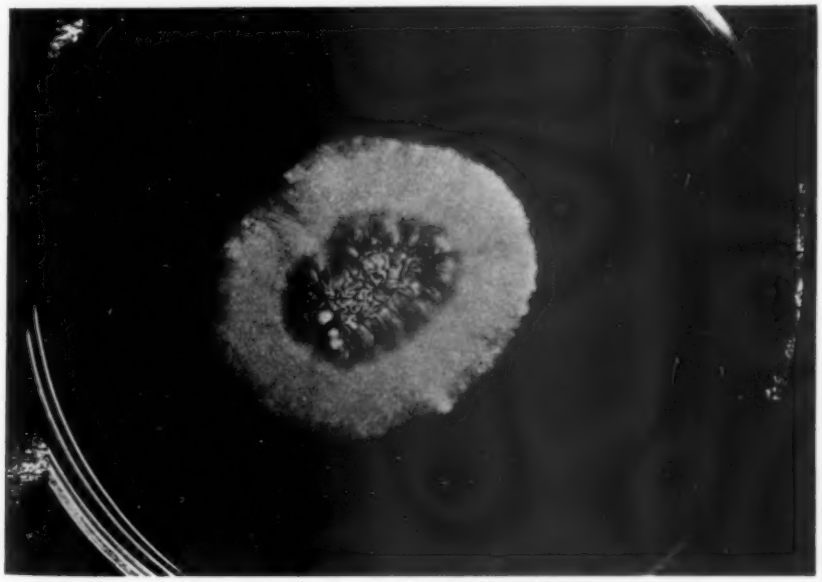

FIG. 4. Colony of *Sporotrichium schenkii* four weeks old. Note the development of pigment.

ally became dark brown. At two months, white excrescences were present on the surface. The young growth had a rubbery consistency tending to friability with increasing age.

Hanging Drop. Hanging drop preparations and specimens made by mixing a small portion of the colony with 15 per cent potassium hydroxide, revealed the grouping of pear-shaped conidia which were present at irregular intervals along the course of hyphae and also appeared as terminal triads and tetrads. Single fructification

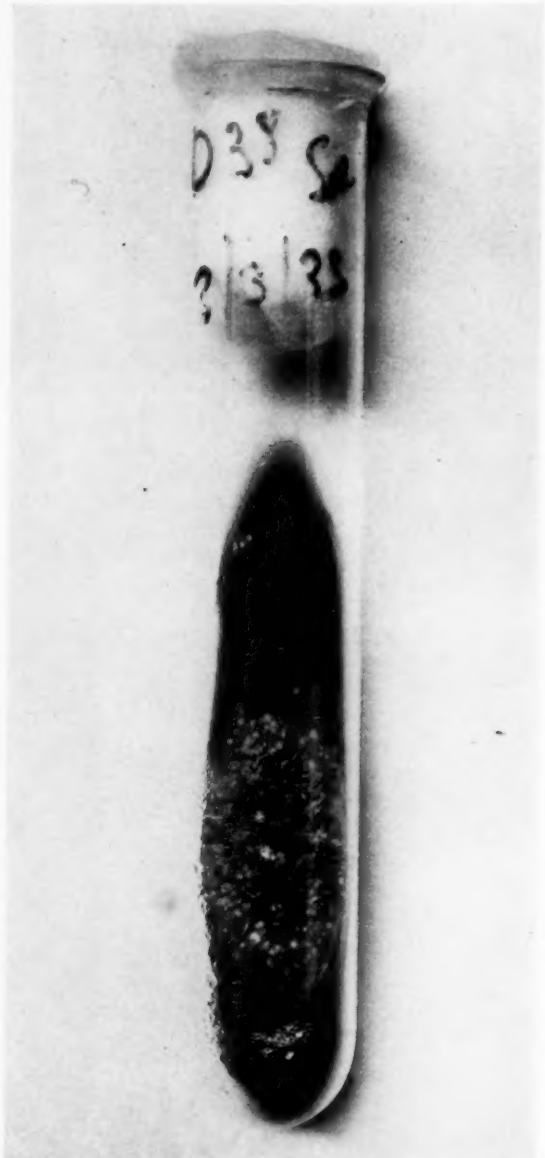

FIG. 5. An older colony of sporotrichium (four months) showing development of white excrescences.

bodies were also observed, attached to the sides of the hyphae. The earlier preparations exhibited a large quantity of fine, branching mycelial threads but in specimens taken from older colonies the picture was dominated by an increased number of spores with very few hyphae in evidence. The diagnosis of *Sporotrichium schenkii* was made.

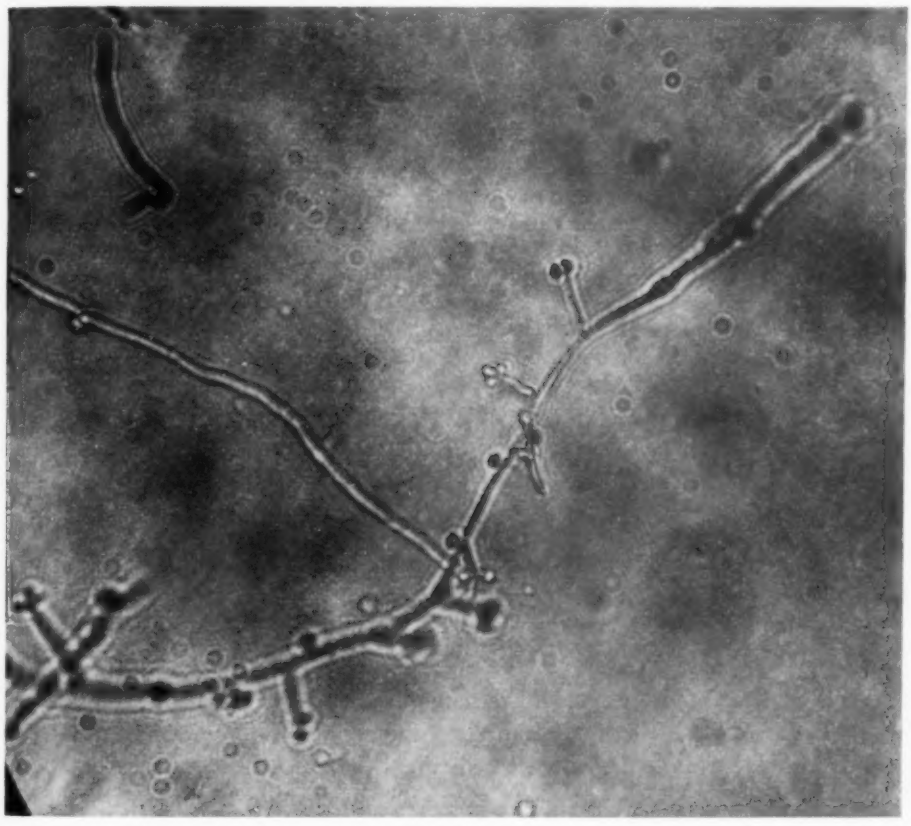

FIG. 6. Microphotograph of a hanging drop preparation made from sporotrichosis colony, showing branching mycelial threads and the development of groups of pear-shaped spores.

Histological Examination. A small portion of the edge of the initial lesion was excised and examined by Dr. David L. Satenstein. His report follows:

"The epidermis is irregularly acanthotic. The greater part of the cutis is filled with a dense cellular infiltrate. The blood vessels are markedly dilated, some approaching the size of sinuses. Scattered throughout the cellular infiltrate are many very small blood vessels. The cellular infiltrate is composed of a great many mast cells, some connective tissue cells, a few plasma cells and in the central portion there is a large group of giant and epithelioid cells. There are also many polymorphonuclear cells scattered throughout the entire zone. There is no degeneration and no abscess formation. The whole process is one of organizing granulomatous tissue with enormous numbers of mast cells. No fungous elements are noted in routine sections, in those stained by Gram's method or by using polychrome methylene blue."

Animal Inoculation. Studies were made by Dr. A. E. Sheplar, who inoculated

a rat intraperitoneally with a saline suspension of a sporotrichosis colony on February 27. The rat was found dead on May 22. The autopsy revealed a small abscess 5 by 5 mm. between the skin and muscles of the abdomen on the same side as the site of the injection. This was filled with cheesy material. The under surface of the stomach showed several pin-head sized nodules. In the peritoneum of the inoculated side were several small abscesses about 2.5 by 2.5 mm. The testes were greatly enlarged (this enlargement was present for one and one-half months), covered with blood (due to hemorrhage three days previous to death), and filled, when incised, with pockets of pus. The other organs of the body appeared normal.

Culture media implanted with pus developed a growth similar in character to the original colony.

Sections were made from the various organs and reported by Dr. Satenstein as follows:

"Sections of all specimens submitted were stained with hematoxylin eosin, Gram's stain, and polychrome methylene blue. No spores or mycelial threads were demonstrated in any of the sections. The lungs, liver, and kidneys showed some congestion, the last named organ also exhibiting cloudy swelling of the tubules. Considerable granular degeneration was present in the central portion and giant cells were observed at the margin of a lymph node. A nodule near the pancreas consisted of granulomatous tissue composed of giant cell tubercles, surrounded by lymphocytes as well as isolated multinucleated cells. The testes, in the sections examined, showed an inflammatory reaction but no breaking down or abscess formation."

Additional Laboratory Examinations. The Wassermann reaction was negative upon two occasions. The white blood cells were 8,000. The differential count showed: polymorphonuclears 69 per cent, small lymphocytes 28 per cent, large lymphocytes 2 per cent and basophiles 1 per cent. The blood sugar determination was 89.25 mg. per 100 c.c. of blood. No tubercle bacilli were found in the pus, and guinea pig inoculations for tuberculosis were negative. Serum sent to the United States Public Health Service was negative for tularemia and undulant fever.

Source of the Infection

It is well known that the organism is a frequent saprophyte on many kinds of vegetation. In his comprehensive report and review of the literature, Foerster [9] found the barberry shrub to be a frequent source of sporotrichotic infection. Benham and Kesten [10] were able to inoculate the organism on carnations causing bud rot. The higher animals are susceptible to the infection and some of the lower animals may also acquire the disease, the rat being particularly vulnerable.

The most common site for the chancre to appear is on the thumb, the index finger and the back of the hand.[11] In our patient, the history disclosed the fact that she had transplanted some cactus plants a few days before the initial lesion was first noticed. She wore rubber gloves to protect her hands and since the first lesion developed on skin proximal to that covered by her gloves the cactus plant came under suspicion. We were, however, unsuccessful in proving this point although we inoculated over a hundred tubes of media with several hundred cactus spines. It is interesting to record that cactus plants were growing in the patient's back yard for the past several years. The original source was unknown. Other plants handled were also investigated without any positive result.

Treatment

Treatment consisted of:

1. Potassium iodide (saturated solution), beginning with 30 minims daily, and steadily increasing to 90 minims daily. At this dosage symptoms of iodism developed. The dose was decreased to 75 minims and then gradually increased to the point of toleration.

2. Roentgen-ray therapy (one and one-half skin units unfiltered) administered to each lesion.

3. Tincture of iodine applied locally.

At the end of two and a half months all lesions were healed. Iodide therapy was continued for a month longer. There has been no recurrence during the past three months.

Summary

A case of sporotrichosis of the localized lymphangitic type is reported from New York where the disease is of rare occurrence. We were able to find the reports of only three other culturally proved cases originating in this state. The organism was recovered on culture, inoculated successfully in a rat and was identified as *Sporotrichium schenkii*. Treatment by means of iodides and roentgen-rays produced a disappearance of all lesions and there has been no recurrence to date. The source of the infection was not determined.

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THE RELATIONSHIP OF SEX TO DISEASE*

By EDGAR V. ALLEN, M.D., F.A.C.P., *Rochester, Minnesota*

THE RELATIONSHIP of sex to disease is frequently so striking that the lack of major interest in this problem constitutes one of the peculiarities of clinical investigation. Many authors presenting this phase of certain diseases either have simply stated that a difference exists in the incidence by sexes, or have explained the difference with an eye on the disease under consideration, but have neglected the broad problem of the relationship of sex and disease. As a result, the explanations given have been in large part inadequate. Those commonly given for the variation in incidence by sex of disease of the gall-bladder and of cirrhosis of the liver are typical. According to these explanations, pregnancy and obesity cause the greater incidence of disease of the gall-bladder among females, and alcoholism explains the predominance of males among those who have hepatic cirrhosis; yet the ratios of females to males are about the same whether one is considering children or adults.[25] Consequently, all the factors given in explanation are valueless, and one's cherished beliefs are shaken.

Early in the course of this study it was apparent that if the surface of the problem were to be more than scratched it would be necessary to examine critically many phases of this interesting relationship. Also, it became obvious that a complete survey of all the aspects of the problem was almost impossible. Such a survey would entail complete examination of all publications dealing with medicine, surgery, pathology and roentgentherapy. All too often the sex of the patient is not stated, terminology varies, and there is reduplication of cases in various reports. Occupation and age influence the distribution of cases according to sex, and these factors are frequently omitted from reports. Even if one could overcome these difficulties, one would find his data of incomplete value. Sex ratio must be corrected by a factor dependent on sex distribution. Unless the ratio of males to females approaches unity in an entire group or population, uncorrected figures of the sex ratio of disease are very misleading. If patients in a given clinic, hospital, or population included twice as many men as women, any disease affecting twice as many men as women would have a corrected ratio of incidence by sex of 1 : 1, whereas uncorrected data would give a ratio of 2 : 1. Hosoi and Alvarez[25] have pointed out that more interest in the relationship of sex to disease may stimulate the compilation of better statistical data, but that the obvious inadequacies of the material available handicap any present study. The absence of accurate data should not unduly discourage the investigator. The chief interest lies in the presence of a pattern, manifested by trends or directions of the relationship of sex and disease. My study shows very

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From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

definitely that such a pattern exists which would in all probability be uninfluenced by more trustworthy data.

Data from The Mayo Clinic, which comprise a large part of this study, are subject in part to correction, since the ratio of males to females for a single year (1926) was 1.03 : 1.[25] However, it is apparent that whenever the uncorrected ratios of incidence by sex are not striking, it is quite possible that they are influenced by the various deficiencies indicated.

I have considered in this study only diseases which affect structures common to both sexes. I have further attempted to exclude diseases and structures, such as carcinoma of the breast, which might be influenced by the different physiologic activities of the two sexes, inasmuch as the function of breast tissue of the female and of the male is different. Similarly, adenomatous goiter has not been studied because adenomas tend to occur in colloid goiters, which are more frequent among females.

Morbidity

Diseases of the Digestive Tract. The excellent reports by Hosoi and Alvarez, and Günther [19, 20] facilitate greatly a study of the incidence by sex of gastrointestinal diseases. A glance at figure 1 shows that males are

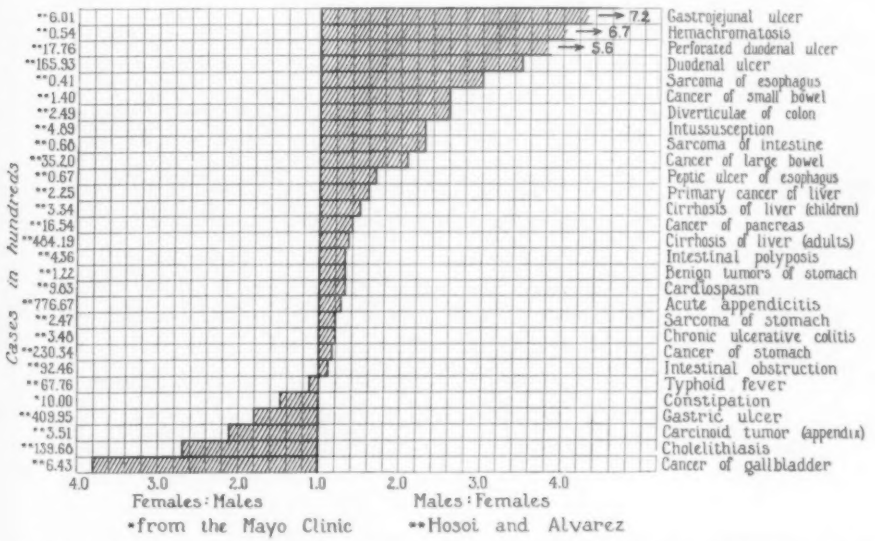

Fig. 1. Diseases of the digestive tract; ratio by sex. Males are preponderantly affected, but cholelithiasis and carcinoma of the gall-bladder are shown to be largely diseases of females.

afflicted with diseases of the digestive tract more than are females. In fact, if gastric ulcer, the incidence of which varies greatly, and constipation, which is really not a disease, were removed from consideration, only carcinoid tumor of the appendix, carcinoma of the gall-bladder, and cholelithiasis remain as diseases affecting the female predominantly. The fact is that the

ratio of males to females, among cases of cholelithiasis, intussusception, and cirrhosis of the liver, is about the same whether one considers children or adults.[25] It is interesting that the tendency of a duodenal ulcer to perforate is almost twice as great in the male as in the female. According to Foshee,[14] chronic gastric ulcer occurs in girls and boys in about the same ratio (ten boys: nine girls). The study of Pack and LeFevre[32] disclosed a high ratio of males to females among patients who had carcinoma of either the esophagus, stomach, colon, rectum, liver or pancreas; in patients who have carcinoma of the gall-bladder, the ratio of males to females is less than 1 : 1.

Diseases of the Lung and Upper Part of the Respiratory and Digestive Tracts. In figure 2 it is shown that of the diseases of this group which have

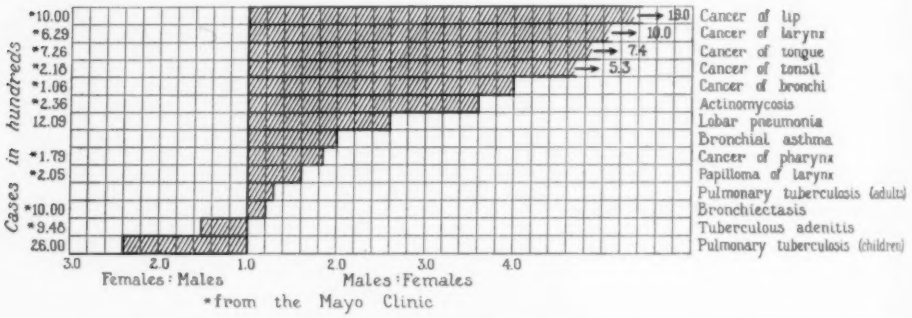

FIG. 2. Diseases of the lung and upper part of the respiratory and digestive tracts; ratio by sex. Only tuberculous adenitis and pulmonary tuberculosis of children affect females more frequently than males.

been studied, only pulmonary tuberculosis in children[31] and tuberculous adenitis affect females predominantly, whereas bronchiectasis, pulmonary tuberculosis of adults,[10] papilloma of the larynx, carcinoma of the pharynx, bronchial asthma, lobar pneumonia,[30] actinomycosis, and carcinoma of the bronchi, the tonsils, the tongue, the larynx and the lip affect males more frequently than females in an ascending degree. The ratio of males to females among patients who have carcinoma of the lip is particularly striking (19.0 : 1) and that of carcinoma of the larynx (10.0 : 1) only slightly less so. Pack and LeFevre found similar ratios for carcinoma of the lip, tongue, pharynx, larynx and tonsils, as well as high ratios of males to females for the incidence of carcinoma of the floor of the mouth, buccal mucous membranes, antrum and superior maxilla, inferior alveolus, nasal septum and parotid gland, and for papilloma of the larynx.

Diseases of the Blood, Blood Vessels and Heart. In this group of cases, only varicose veins and chronic mitral endocarditis affect females more frequently than males (figure 3). Considering the former disease, the ratio of females to males is high, probably because of the venous obstruction incident to pregnancy, and because of the great amount of subcutaneous fat which furnishes poor supporting tissue in the female. The high comparative incidence of valvular heart disease among females may be due to their greater

susceptibility to chronic arthritis, although such a condition is not commonly associated with valvular heart disease. The cases of chronic adhesive pericarditis are from the report of Smith and Willius,[36] who selected the cases on the basis of records of postmortem examination. The high ratios of

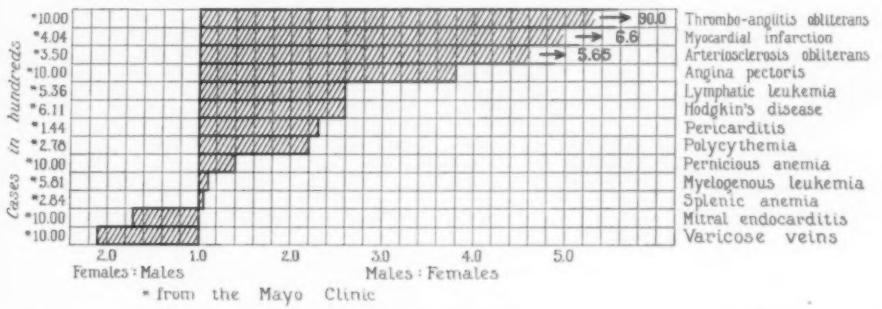

FIG. 3. Diseases of the blood, blood vessels and heart; ratio by sex. The high incidence of diseases of the peripheral arteries and heart among males is striking. The term arteriosclerosis obliterans is used to denote sclerosis and occlusion of the peripheral arteries.

males to females in the incidence of thromboangiitis obliterans, myocardial infarction, occlusive arteriosclerotic disease affecting the extremities, angina pectoris, lymphatic leukemia, Hodgkin's disease, and polycythemia are striking. Günther[21] has expressed the belief that diseases of the arteries occur more frequently among men, whereas diseases of the veins occur more frequently among women.

Although syphilis is not, strictly speaking, a disease of the blood, it is convenient to consider it under this heading. An excellent report of the incidence by sex of this disease has been given by Turner,[40] who studied 10,000 cases, in 5,017 of which the patients were males and in 4,983, females. His figures for syphilitic meningitis, syphilis of the skin and mucous membranes (taken together), cardiovascular syphilis, syphilis of the central nervous system, general paresis and tabes dorsalis show that the ratio of males to females is 2.0 : 1, 1.0 : 1, 2.8 : 1, 2.2 : 1, 3.0 : 1, and 4.9 : 1 respectively. Syphilis affects the skeletal system of males more commonly than that of females. The ratio of females to males for latent syphilis is 1.7 : 1.

The greater immunity of the female to syphilis has been the subject of a treatise by Warthin,[41] who has reviewed the possible causes of such comparative immunity. He felt that perhaps: "The *Spirocheta pallidum* is a pathogenic descent of some harmless spirochetal form inhabiting the female body ages ago, and in consequence woman establishes a more comfortable partnership with this organism than does man." Pregnancy also appears to influence favorably the course of a syphilitic infection. However important these explanations are, the fact remains that most other diseases also affect men more commonly. The explanation is probably valid in all instances and constitutes one which I shall consider more in detail later.

Diseases of the Bones, Joints and Urinary Tract. Of this group of dis-

eases only chronic infectious arthritis* and nonstructural backache affect women more frequently than men (figure 4). The latter disease may occur

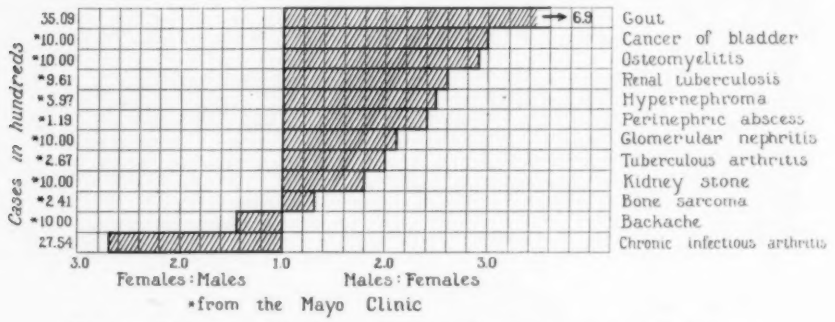

FIG. 4. Diseases of the bones, joints and urinary tract; ratio by sex.

among women more commonly, because it may be a manifestation of nervousness and chronic fatigue, or because of pathologic or abnormal physiologic conditions concerning the female organs of reproduction. The incidence of malignancy involving the osseous and urinary tracts is greater among males, as is the incidence of carcinoma elsewhere in the body. Pack and LeFevre found the following respective ratios of males to females for papilloma of the bladder, carcinoma of the bladder and hypernephroma: 2.0: 1, 3.4: 1 and 2.0: 1. Although the incidence of pulmonary tuberculosis among adults is greater in males than in females (figure 2), the difference in incidence for the two sexes is less than that seen in renal tuberculosis. The figures on gout are those of Hench,[22] who collected 3,509 cases from the literature. Hench believes the ratio given in figure 4 is much too low, for the diagnosis as applied to females was frequently erroneous. The ratio for cases observed by him was 40.0 males to 1 female. Ehrström[13] gave for gout, a ratio of males to females of 20.0: 1.

Miscellaneous Diseases. The ratios for most of the diseases in this group (figure 5) are not striking. Obesity, pityriasis rosea, and urticaria

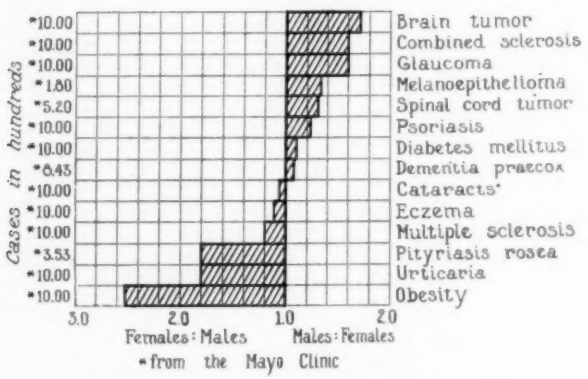

FIG. 5. Miscellaneous diseases; ratio by sex.

* Data from the American Committee for the control of rheumatism.

affect females more commonly than males. Tumor of the brain, combined sclerosis of the posterior and lateral columns of the spinal cord, and glaucoma, are predominantly diseases of males. The high ratio of combined sclerosis is due in part to the greater incidence of pernicious anemia (figure 3) among males. Obesity may affect females more frequently because of their more sedentary life, and because of their frequently abnormally large appetite in pregnancy. Pack and LeFevre have shown that adenomatous goiter affecting males is more likely to become carcinoma than when affecting females. Breitner and Just[3] found that carcinoma develops among 3.8 per cent of females and 5.8 per cent of males who have nodular goiters.

Functional Nervous Diseases. This is the single group of diseases in which females are affected more frequently than males (figure 6). Some

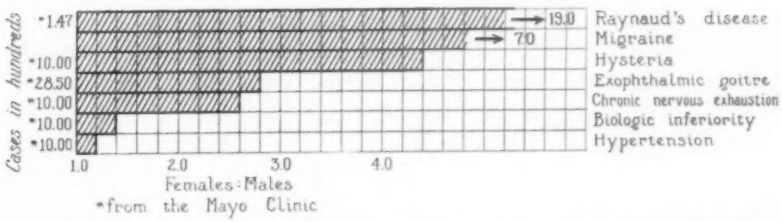

FIG. 6. Functional nervous diseases; ratio by sex. All of the diseases studied have a higher incidence for females than for males. Therefore, there is no space in the figure representing diseases which affect males predominantly.

objection may be raised to the inclusion of Raynaud's disease, exophthalmic goiter, and hypertension in this group of cases. However, Allen and Brown[1] have indicated the functional nature of Raynaud's disease; exophthalmic goiter appears to be a manifestation of imbalance of the sympathetic nervous system, and essential hypertension in its early stages is definitely an evidence of disturbance of the sympathetic nervous system. The factors explaining the predominance of exophthalmic goiter among females have been discussed by Gardiner-Hill.[23] Riseman and Weiss,[35] in a review of the ratio by sexes in hypertension, found figures greatly at variance. In their series, 30 per cent were males. Draper[12] stated that of patients who have migraine, the ratio of females to males is 7.0:1; among 1,000 cases seen at The Mayo Clinic, it was only 2.1:1. An interesting side light on the incidence of nervous disturbances by sexes was furnished by Gaupp,[16] who noted that four men committed suicide to each woman, although women made more suicidal attempts ("nicht ernste gemeinte!"). The distribution of diseases of the nervous system by sex has been furnished by Günther.[18]

Comment. The study, thus far, has dealt with morbidity, and it appears that the male is less favorably situated as far as most of the diseases under consideration are concerned. However, I have been dealing with a highly selected group of diseases, such as would bring the patients long distances to large medical centers. A survey of all the illnesses in a community, or among large numbers of people under observation, might give entirely

different results. Sydenstricker[37] has shown, in such a study, that the male ratio of sickness is consistently less than that of the female. The records of Leipzic Local Sick Fund for the period of 1887 to 1905, covering the illnesses of 259,582 females and 952,674 males, show that the incidence of sickness among females was definitely greater than that among males up to the age of 55 years, after which the reverse was true.[37] Similar results were found in a study by the Metropolitan Life Insurance Company, dealing with 376,573 persons, except that the incidence of sickness among females was found to exceed that among males only up to the age of 45 years.[37] Sydenstricker's study of the children of Hagerstown, Maryland, disclosed that the incidence of most diseases among children under five years of age was higher among boys than among girls, but that in adolescence there was a higher incidence among girls for all diseases for which comparisons are warranted.[38] Collins, who studied 5,071 school children, found that the incidence of sickness was consistently higher for girls than for boys.[9] Britten found that rates of physical impairment are on an average higher for women than for men.[4] The figures of 935 German Krankenkassen for 1930 are at variance with those just given. Among the 2,500,000 members there were 45.8 cases of illness for each 100 men, and only 40.7 cases for each 100 women.[26] These are insurance figures, difficult of evaluation because of the influence which sick benefits have on the number of claims of illness, and inasmuch as they contradict the experiences of other investigators, are probably influenced by peculiar circumstances. Britten's study of the influenza epidemic revealed inferior resistance of the male.[5] The incidence of influenza was distinctly greater among females, but the mortality was higher among males.

The available data, then, indicate that females are sick more than males. However, my study shows that among males there is a higher incidence of most diseases which might permanently influence health or endanger life.

Mortality

It occurred to me that if the conclusion just reached was entirely justified, the predominant morbidity ought to have a well marked influence on the mortality rates. The sources of my studies on mortality were the reports of the United States Bureau of Census and the United States Mortality Statistics.[15, 29] I have used the compiled data of 1920 in both instances, for no census report has been published since this date. It is obvious that the mortality figures for the same year must be used in order to secure the ratio of deaths to the entire population. The mortality among males is higher than that among females with the exception of persons aged 20 to 34 years, inclusive, when the death rate among females is higher, apparently due to the mortality from childbirth.* The ratio of males to females (deaths of males

* Senior Statistician Britten of the United States Public Health Service has pointed out to me that the increased mortality for females in the age group mentioned was true in 1920 but not true in 1900, 1910 or 1930.

for each 100,000 males/deaths of females for each 100,000 females) is shown in figure 7, and indicates the increased mortality for males in all periods of life except during the inclusive ages of 20 to 34 years.

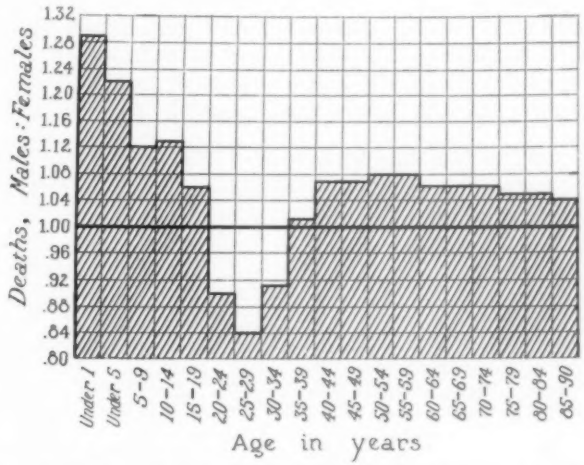

FIG. 7. Ratio of deaths of males among each 100,000 males to deaths of females among each 100,000 females in the registration area of the United States for 1920. The mortality for males is more than one in all age groups with the exception of the inclusive ages of 20 to 34 years. The calculation by which the ratio was obtained is explained in the text.

Further evidence of the higher mortality among men is the expectancy of shorter life for them. Wiehl's[42] figures for 1927 show that at the age of 10 years females can expect 55.32 years of life, and males only 51.88 years. According to this author, the expectancy for life of persons who reach maturity actually decreased between the years of 1921 to 1927, due to the greater mortality among men. Wiehl also showed that mortality begins earlier in life for men than for women. Bakwin[2] has shown that the decrease in infant mortality has been greater for females than for males.

Since the rate of death among males is higher than that among females, the ratio of males to females in the entire population ought to show a resulting shift. Actually this is the case. Males outnumber females in the total population at all ages up to 20 years, when the female population is greater. The difference, although slight, persists during the ages of 25 to 29 years inclusive, when the number of males again exceeds that of females, with a rough parallelism occurring until the age of 55 years. At this point there is a gradually diminishing predominance of males in the population of the United States, until, at the age of 75 years, the females outnumber the males and continue to do so. Therefore, when the age of 100 years is reached, there are almost twice as many females as males.

This study now allows several conclusions. It appears that females are sick oftener but less seriously than males; but that most serious diseases are contracted by a higher proportion of males; that the rate of mortality is uni-

formly higher for males than for females, with the exception of the age period of from 20 to 34 years inclusive; that this increased mortality influences the entire population, so that the ratio of females to males in the registration area of the United States gradually increases from the age of 55 years onward, and that the expectancy of males at the age of 10 years is less than that of females by about three and a half years.

The factors which are usually set down in explanation of the greater mortality of males are overwork, alcoholism, venery, tobaccoism, exposure to the elements, industrial hazards, and irregular habits of eating and sleeping. It occurred to me that the validity of such an assumption could be tested by selecting patients who were subject to none of these factors. Consequently I have studied (1) intra-uterine mortality; (2) congenital deformities, and (3) mortality in the early years of extra-uterine life.

Intra-Uterine Mortality. Holmes and Mentzer[24] have shown that from 103 to 108 males are born for each 100 females, depending on the population studied. The mortality rates for males during intra-uterine life is consistently predominant, varying with the different months after conception, from 375 to 118 males for each 100 females. These are important figures, having to do with a group of persons far removed from the influences usually advanced as explanations of the greater rate of mortality among males. Here are data so striking as to seem erroneous were it not for the fact that they fit so easily into the pattern which is beginning to form. Here is evidence that the male is fundamentally the weakling of the two sexes.

To digress from the subject of mortality for a moment: Congenital deformities are tremendously predominant among males. The ratios (male to female) for congenital pyloric stenosis, Meckel's diverticulum, Hirschsprung's disease, esophageal diverticulum, harelip, cleft palate and renal agenesia[8] are 3.9:1, 3.7:1, 3.3:1, 2.1:1, 1.6:1, 1.5:1 and 1.2:1, respectively. Here again are astonishing data, the validity of which can be tested by a study of mortality in the early years of life.

Mortality in the Early Years of Life. In the registration area of the United States in 1920, 8,500 males and 6,700 females died for each 100,000 males and for each 100,000 females, respectively, of that part of the total population which is less than one year of age. The corresponding figures for that part of the population less than five years of age were 2,300 and 1,900, respectively. The ratio of males to females (deaths of males per 100,000 males/deaths of females per 100,000 females) for that part of the population less than one year of age was 1.29:1 and for the population less than five years of age it was 1.21:1 (figure 7). The data for infants less than one year of age are excellent for comparison, inasmuch as both girls and boys lead their existence largely in a crib; boys receive diets no different from girls, and both are equally protected from extraneous factors which might influence mortality. Yet the corrected ratio of mortality for boys to girls is 1.29:1. The lives of boys and girls who are less than five years of

age are practically identical, aside from the fact that boys are possibly more subject to trauma by virtue of their greater activity, and are more exposed to infectious disease because of their wider contacts. Yet these factors, if they are present, influence the mortality of males favorably rather than unfavorably, for the corrected ratio of mortality for boys to girls is 1.21 : 1; less therefore than that for infants less than one year of age.

General Comment

The present study indicates that serious disease involving structures common to both sexes afflicts males oftener than females. That this is not due to some habit or habits of life peculiar to the male is indicated by the greater male mortality rate during intra-uterine life, and for the first five years of extra-uterine life, as well as by the predominance of congenital deformities among males.

The mechanism and cause of this inherent weakness of the male are difficult to explain. Clarke [7] felt that inasmuch as males are larger than females at birth, intra-uterine nutrition would be more difficult and birth injury would be more common; and that latent effects of unrecognized birth injury might account for the difference in mortality later. One might predicate that a wise Nature, knowing males to be numerically less important in the scheme of reproduction, is less careful of them, but it is strange that she should allow them to be conceived in superabundance, only to begin immediately to reduce their number by death.

There is considerable evidence that the male is more highly differentiated from the neuter or species type than is the female.[27, 34] Castration of the male produces far more extensive effects than does castration of the female. Furthermore, the castrated male takes on characteristics which are in many respects similar to those of the female. The gist of this hypothesis is that the male, representing advanced or more specialized development, is more susceptible to disease, in the same way that all organisms having highly specialized tissues are more susceptible to derangement than are simple unicellular organisms.

The metabolism of males, according to Draper, is 2 to 4 per cent higher than that of females. This difference is illustrated by the fact that whereas the egg is large, quiescent, and stores up energy, the sperm is small, active, and spends energy. Geddes and Thompson [17] have felt that femaleness is characterized by preponderant anabolism and maleness by preponderant catabolism. This increased catabolic tendency of the male might well influence his resistance to disease. Whatever the explanation for the influence of sex on disease may be, it appears incontrovertible that there exists a sex-linked inferiority of the male; that mere maleness influences unfavorably the resistance of the organism to disease during all ages.

One might object to the hypothesis that susceptibility to disease is determined along with sex [11, 28, 33] only to be held quiescent for the many years be-

tween conception and the appearance of the disease; yet examples are common in medicine. An inherited tendency to baldness, hypertension, abnormal arteriosclerosis, and even brevity of life or longevity, may remain unrecognizable for years, only to come into view at a period of life which careful study of family records would have allowed one to predict.

For each explanation of the lack of inherent vitality of the male there are objections, but these do not influence the fact; the male is, by comparison with the female, a weakling at all periods of life from conception to death. Venery, alcoholism, exposure, overwork, and various other factors may influence the susceptibility to disease and the greater mortality of the adult male, but they are only straws placed on the greater burden of his sex-linked weakness. There seems to be no doubt that, speaking comparatively, the price of maleness is weakness. How ironical therefore seems the precept of the apostle (I Peter: I, 13): "Give honor unto the wife as unto the weaker vessel."

The possible facts brought out by this study are worthy of further investigation. The results of various therapeutic endeavors need to be carefully studied from the standpoint of how they are influenced by sex. W. J. Mayo has stressed the comparative seriousness of certain diseases when they affect males instead of females. More studies of the differences in physiologic and chemical processes of the two sexes are urgently needed,[6, 39] and there is a crying need for better medical statistics. Only in these ways can the full effect of sex on disease be adequately investigated. Finally, the therapeutic implications should not be overlooked. Hemophilia, purely a disease of the male, usually can be adequately controlled by ovarian therapy. The use of preparations of organs which determine the sex characteristics of the female may, in the future, be found of value in the treatment of thromboangiitis obliterans, angina pectoris, gout and arteriosclerosis, while the sex glands of the male given therapeutically to the female may favorably influence Raynaud's disease, migraine, and functional nervous disturbances.

Certainly this interesting phase of medicine has been too much neglected. It is to be hoped that the future will witness gratifying progress in the study and understanding of the fascinating problem of the relationship of sex to disease.

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HYPOGLYCEMIA AND HYPERINSULINISM *

By Milo K. Tedstrom, B.S., M.D., F.A.C.P., *Santa Ana, California*

Hypoglycemia is not a disease entity, but a symptom complex, and is defined as a deficiency of blood sugar. There is considerable difference of opinion as to what constitutes a normal blood sugar, and there is marked variation in the level at which hypoglycemic symptoms are noted. Joslin [46] states that the average normal fasting blood sugar is 100 mg. per 100 c.c. of blood.

In 1924, Seale Harris [18] reasoned that since other endocrine glands, notably the thyroid, adrenals, pituitary, etc., showed both hypo- and hyperfunction, the islet cells of the pancreas would probably show similar variation in function; he soon found three cases with low blood sugars and with symptoms similar to those produced by injection of an excess of insulin.

In order to make clear the factors involved in maintaining a normal blood sugar level I shall briefly state them.

It is generally recognized that hepatic glycogen is the chief source of blood sugar. When food is being absorbed the blood sugar is temporarily increased. The internal secretions of the ovaries, testes and parathyroid act with insulin to reduce blood sugar, while the secretions of the pituitary, thyroid and adrenals tend to raise blood sugar. The interaction of these hormones may be controlled through a nervous center probably located in the pons, according to MacLeod.[42]

The following classification (table 1) of spontaneous hypoglycemia is based chiefly on an analysis of reported cases:

It is not our purpose to discuss the entire subject of spontaneous hypoglycemia but to limit our remarks to those cases of pancreatic origin or so-called hyperinsulinism.

Gray and Feemster,[43] in 1926, found diffuse hypertrophy of the pancreatic islets in a child born of a diabetic mother. This child died in hypoglycemic shock. De Takats and Wilder [44] have shown that hypertrophy of islet tissue follows trauma to the pancreas. This hypertrophy is accompanied by an increased function of the isles of Langerhans.

In 1928 Finney and Finney [35] resected a large portion of a morphologically normal pancreas in a patient with hypoglycemia, with some improvement in symptoms. Since Finney and Finney's resection of a normal-appearing pancreas the same operation has been done in five other similar cases with varying results.

* Read before the General Medicine Section of the California Medical Association at the sixty-second annual session, Del Monte, April 24 to 27, 1933.

From the Johnston Clinic, Anaheim, California; and St. Joseph Hospital, and Orange County Hospital, Orange, California.

TABLE I

SPONTANEOUS HYPOGLYCEMIA

(A) Glandular

- Pancreatic
  - Hyperinsulinism or Dysinsulinism
    - Adenoma
    - Carcinoma
    - Functional or Neurogenic Hyperplasia and Hypertrophy of islets
  - Hypoglycemia of late diabetes
  - Alimentary hypoglycemia
- Adrenals
- Pituitary
- Thyroid
- Parathyroids
- Hepatic
  - Toxic hepatitis
  - Cirrhosis of liver
  - Acute yellow atrophy
  - Carcinoma
- Ovary
- Pluriglandular

(B) Other Causes

- Renal diabetes
- Lactation and pregnancy
- Toxemias of pregnancy
- Vomiting of childhood and convulsions
- Excessive fatigue or physical exhaustion
- Scleroderma
- Muscular dystrophy
- Terminal hypoglycemia
- Fasting
- Status lymphaticus
- Bronchial asthma

The failure to demonstrate any pathological changes in nine pancreases examined at operation or after death is analogous to the failure to demonstrate changes in the islets of some diabetics. There is probably a nervous imbalance resulting in hyperinsulinism, or it may be that small adenomata are present but not found.

The first pathological study of hyperinsulinism due to carcinoma of the pancreas was reported by Allan and associates [19] in 1927. A physician, 42 years of age, with hypoglycemic symptoms associated with a lowered blood sugar was operated on at The Mayo Clinic. A carcinoma of the pancreas with metastasis to the liver was found. Later at autopsy insulin was extracted from the pancreatic growth and the liver nodules. One other case of fatal hypoglycemia has been reported as secondary to carcinoma of the islets.

Adenomata of islands of Langerhans have been removed in seven cases with relief of symptoms, and have been found post mortem in three patients dying in hypoglycemic coma. Graham and Womack [40] have just reported a remarkable case of hypoglycemia with many neurological symptoms and signs. They operated on this patient and removed a single adenoma. Because the patient did not improve, and in fact became much worse, a second operation was done and a second adenoma was found. This latter one was not visible but was felt by palpating the pancreas between the thumb and index finger. Removal of this tumor resulted in relief of hypoglycemia and the accompanying symptoms. John [26] has reported a fatal case of

hypoglycemia in which the pathological examination revealed both an adenoma of the pancreas and a carcinoma of the liver.

TABLE II

Pathology of 68 Analyzed Cases of Spontaneous Hypoglycemia [1–41]

	Total No. of Cases	Diagnosis: At Autopsy	Diagnosis: At Operation	Diagnosis: Clinically	Operative Procedure
Hyperinsulinism or dysinsulinosis	53				
A. Functional (Normal pancreas pathologically)	38	2	7	29	6 Removal of portion of pancreas
B. Adenoma (benign)	10	3	7		7 Removal of adenoma
Adenoma (malignant)	1		1		
C. Carcinoma of islets	1	1			
D. Carcinoma of islets and metastasis to liver	1	1		Insulin extracted from nodules in liver	
E. Adenoma of pancreas and carcinoma of liver	1	1			
F. Faulty starch digestion	1			1	
Associated with uremia	2	2		Hyperplasia and hypertrophy of islets in one case	
Hepatic					
A. Carcinoma of liver	3	3			
B. Acute yellow atrophy	1	1			
C. Tumor (in child)	1	1			
D. Cyclic vomiting	4			4	
E. Toxic hepatitis { Neosalvarsan	1	1			
E. Toxic hepatitis { Cincophen	1			1	
Carcinoma of adrenals	1	1			
Hypo-adrenalism or pluriglandular	1			1	

All adenomata of the pancreas are not accompanied by hypoglycemia, just as all adenomata of the thyroid are not accompanied by hyperthyroidism.

The symptoms of spontaneous hypoglycemia are essentially the same regardless of the underlying pathology; and they are not necessarily in direct proportion to the blood sugar level. There is, however, considerable individual variation in symptoms. Some patients will exhibit mild symptoms with a blood sugar level of 80 to 90 mg. per 100 c.c. of blood, while others will not show symptoms with blood sugar between 50 and 60 mg. In general, however, the lower the sugar level the more severe are the symptoms.

It is recognized that an analysis of the symptoms of reported cases probably is not an accurate index of all the symptoms noted in the individual cases, as some of the reports are very brief. However, such an analysis may serve to show the relative frequency of the various symptoms associated with hypoglycemia. The frequency of the various symptoms occurring in 65 cases [1–41] is shown in table 3.

The most frequently observed symptom of hypoglycemia was extreme weakness, expressed as such or as excessive fatigue, or tiring or exhaustion, both mental and physical. Nervousness, muscle tremors, vertigo, excessive sweating, headaches, and a sensation of excessive hunger often accompanied this weakness, and as attacks became more severe, drowsiness, stupor, fainting or even coma, were observed. The coma might be of sudden onset and the first symptom noted.

TABLE III

Symptoms of 65 Analyzed Cases [1-41]

Stupor 7, Coma 39		46	Loss of memory 20
Weakness or prostration 37, Fatigue or tiring 10		47	Diagnosis of epilepsy 14
Muscular twitchings 8, Convulsions 26		34	Vertigo 10
Sweating		19	Hunger (Excessive) 12
Change of general behavior		18	Dulness and listlessness 10
Speech disturbances	Slow 3, Monotonous 1, Unintelligible 8, Motor aphasia 5, Slurring 1	18	Fainting 8
Nervousness		15	Tremors 8
Eye symptoms	Diplopia 5, Dimness of vision 3, Dilated pupils 2, Blurred vision 1, Unequal and miotic pupils 1	12	Headache 9
Mental confusion		14	Epigastric pain 8
Restlessness 8, Maniacal 7		15	Babinski 8
			Nausea and 3, Vomiting 7	10
			Drowsiness 9
			Vague paresthesias 6
			Loss of sphincter control 5
			Irrational 5
			Foaming at mouth 4
			Emotionally unstable 5
			Fear of death 3
			Pallor 4

Coma might be unaccompanied by other symptoms but was frequently accompanied by muscle tremors or by localized or generalized convulsions. The convulsions were generally of the clonic type. Biting of the tongue has been reported in only two cases; it was also noted in the writer's case 2. A loud cry preceded the convulsions in a few instances. Foaming at the mouth was occasionally noted. An aura of weakness, faintness, uneasy feeling, or excessive hunger might precede the convulsion. Spontaneous cessation of convulsions usually occurred after a few minutes. A prolonged sleep might follow the convulsive seizure. The deep reflexes have been variously reported as absent, hyperactive or decreased during attacks. A positive Babinski sign has been frequently observed. This sign disappears and the reflexes generally return to normal with elevation of the blood sugar level.

Eye symptoms and speech disturbances were often noted. A marked change of general behavior, mental confusion and amnesia were commonly observed. Many of the patients were extremely restless and, as the blood sugar level became lower, some became violent or maniacal and were restrained with difficulty. Often the phrase "resembling alcoholic intoxi-

cation " was used in describing such symptoms. Neurological symptoms of varying severity were noted in almost every case and frequently led to a diagnosis of some neurological disorder. Other less frequently observed symptoms were disorientation, dulness, apathy, vague paresthesias chiefly of the face or extremities, irrationality, and crying. Loss of sphincter control was not infrequently described. A fear of impending death was occasionally noted. One patient had attacks typical of coronary disease with typical electrocardiographic findings, over a period of many months. The attacks ceased and the electrocardiograms became normal with elevation of the sugar level. Simple tachycardia or dyspnea was frequently observed. Repeated attacks of paroxysmal tachycardia were observed in one patient during the hypoglycemic state.

The convulsions associated with hypoglycemia resemble true epileptic seizures so closely that a diagnosis of idiopathic epilepsy had been made 14 times in this series of cases. There must be a definite relationship between epilepsy and the blood sugar level, as Joslin [47] has not observed a single case of true epilepsy in 5,086 diabetics and Wladyczko [45] has reported a marked increase in epilepsy in Russia at a time when sugar was scarce. Carbohydrate feedings of those patients with hypoglycemia and convulsions resulted in the attacks becoming fewer and milder. Since many of these individuals have been freed of their convulsions by proper diet or by surgical correction of the underlying cause of the hypoglycemia, every case of epilepsy should have blood sugar studies.

Two cases have been reported in which epileptic convulsions were noted chiefly at menstruation. The writer's case 2 had more frequent and severe convulsions on the first day of menstruation. Case 4 of the writer's was usually quite well except at menstruation, when symptoms attributed to hypoglycemia were noted. Case 3 showed more marked hypoglycemic symptoms the first and second days of menstruation. She had a blood sugar of 38 mg. and 40 mg. following a glucose test meal given the first day of her menstruation. At these levels she was very nervous, restless, and very drowsy. Two days later she had a normal sugar tolerance.

A study of fasting blood sugars and sugar tolerances taken between and during menstrual periods is now being made on a series of patients. Full reports will be published at a later date, but preliminary studies indicate that there is a lowering of the blood sugar the first day of menstruation. These preliminary studies also indicate that some of the menstrual pains, sensations of weakness, nervousness, fatigue, etc. may be controlled by the administration of carbohydrate.

The frequency of attacks and time of occurrence vary considerably. The majority of the attacks occurred during the night or early morning. Attacks were usually before meals, especially in the late afternoon three or four hours after the noon meal. They might occur during a meal. Light meals, omitting meals entirely, irregular eating hours, or exertion frequently provoked an attack. Attacks might occur several times a day in more

severe cases, or daily, weekly, or monthly in milder cases. They usually increased in frequency and severity.

Carbohydrate feedings will usually prevent, relieve or abort the attacks unless they are due to hepatic disease. Adrenalin will relieve some attacks, especially if glycogen is available. Pituitrin gives less relief.

Sugar tolerance curves following glucose test meals were reported in 40 of the 65 cases. Of these, 14 curves were essentially normal, 23 curves were low, and 3 were of the diabetic type. The lowest sugar level was noted three hours following the meal in 14 cases, and four to six hours following in 12 cases. Low fasting sugars were noted in only 18 cases. However, either a low fasting sugar or a low sugar three to six hours following a glucose meal was noted in almost every case.

It is quite important that the tolerance curves be extended through a period of five or six hours after the test meal, as not infrequently a low sugar reading will not be obtained if sugar determinations cease at three hours.

The results of adrenalin tolerance tests or of the use of adrenalin during attacks were reported in 17 cases. There was no response following adrenalin or pituitrin in one case of hepatic carcinoma, and in one case of adrenal tumor. Of the 14 cases with elevated sugar curves following adrenalin, three had adenomas of the islets. Hypoglycemia in one was said to be due to pluriglandular defects, and in 10 to hyperinsulinism. The response to pituitrin was good in three cases of hyperinsulinism and slight in one.

Of the 65 analyzed cases 41 were males, 19 females, 4 children, and one adult whose sex was not stated. The ages range chiefly from 20 to 60 years.

The diagnosis of hypoglycemia rests almost entirely on blood sugar studies. Fasting specimens, specimens taken when symptoms are present, and glucose tolerance tests usually furnish sufficient data to make a diagnosis of spontaneous hypoglycemia. The relief of symptoms by eating, or by glucose intravenously, proves these symptoms to be due to a lowered blood sugar. There seems to be no clinical picture that might differentiate hypoglycemias secondary to pancreatic tumor, from those due to benign hyperplasia, or to hyperfunctioning, normal-appearing islets. The number of cases in which it has been possible to interpret the meaning of the sugar tolerance curve in the light of knowledge of the pathological changes in the pancreas, determined at operation or autopsy, is still too few to permit of definite conclusions, but there does appear to be a tendency to a lower glucose tolerance curve in functional hyperinsulinism. Hyperinsulinism secondary to pancreatic tumor is apparently more difficult to control than that due to hyperplasia or functional changes in the islets, and the hypoglycemic attacks in the tumor cases seem to increase in frequency and severity more rapidly.

Treatment is both medical and surgical. The treatment during an attack consists of giving carbohydrate by mouth or intravenously. Twenty-five grams of glucose are usually sufficient when given intravenously. Adrenalin or, less frequently, pituitrin, hypodermically may check the attack. Ephedrin has apparently been valueless.

When the hypoglycemia is due to functional hyperinsulinism and attacks are mild, extra carbohydrate feedings may control symptoms very well. If attacks are only in the early morning hours, a carbohydrate feeding late the previous evening will usually prevent them. A high-fat, low-carbohydrate diet is usually best, as this tends to decrease secretion of insulin and thus check the hyperinsulinism. In cases that are not controlled by high-fat diet it may be necessary to resort to a moderately high carbohydrate diet with between-meal feedings of carbohydrate. Theoretically, the higher carbohydrate diets would seem to cause increased secretion of insulin with continued overwork of the pancreas and resulting diabetes mellitus or hypoinsulinism.

If adrenalin relieves attacks, suprarenal extract by mouth may be of considerable aid in elevating blood sugar level. Pituitrin seldom causes sufficient rise in blood sugar to be of any benefit.

It does not seem wise to resort to surgical treatment unless symptoms are increasing or cannot be controlled by dietary régime. Surgery has given excellent results in cases where adenomas have been removed, and there have been no deaths. Cases in which resections of portions of the pancreas have been done have, with one exception,[40] not received sufficient benefit to justify the surgical procedure. It is probable that not enough of the pancreas has been removed, or that small adenomas have been present but have not been found.

Case I

T. C., age 49, male; first seen by me in June 1932, because of frequent attacks of loss of consciousness.

His first attack was on the afternoon of April 14, 1931. At this time he suddenly became violent and unmanageable. Members of his family could not control him. With the aid of three men he was placed in an ambulance and brought to the Orange County Hospital. Shortly after arriving at the hospital he was apparently normal, being conscious and quiet. He had no recollection of the previous attack or of being brought to the hospital. The next day he was again unconscious. Nurse's note stated, "Patient's temperature, pulse and respiration normal; patient apparently normal but am unable to arouse him." He remained in coma about 36 hours, when he suddenly aroused. He stated that he had noted for some time that he was frequently drowsy and that he seemed more tired and weaker than usual. He had noticed that if he ate a heavy meal he felt all right, but if he did not do so he felt tired and his "strength seemed to go away."

Following the above attack he continued to have similar attacks of coma occurring every two or three days and lasting from one to thirty-six hours. They were usually unaccompanied by other symptoms. They would disappear spontaneously and he would have no recollection of them. Consciousness could always be restored by intravenous glucose. Occasionally he would be maniacal, difficult to manage, would refuse to do anything. He had to be put in restraint at times. During some attacks there was loss of sphincter control, the patient's body was rigid, and occasionally slight jerking of the muscles over the whole frame was noted. Actual convulsions were never seen. Extreme restlessness and moaning and groaning were occasionally noted with stupor. Frothing at the mouth and profuse sweating were seen in some of the attacks. Breathing was stertorous.

Between attacks he was usually quite well, except for a vague weakness.

During mild attacks, speech was very slow and monotonous. In more severe attacks he would say only one word, usually a slow "yes." Speech at times would be unintelligible. The pupils were small, regular, and reacted to light and accommodation. The reflexes were normal at all times. A positive Babinski sign was never noted. The general physical examination was always essentially negative. Blood pressure was 140 systolic and 80 diastolic. The pulse was usually slow (60), and the temperature subnormal, 96° to 97° in attacks. A roentgen-ray of the sella was negative.

The patient has been seen in coma with a blood sugar of 60 and also with one of 48 mg. He also has been observed with a blood sugar of 42 mg. without any symptoms. The fasting blood sugar ranged from 42 mg. to 100 mg. Blood Wassermann was negative but spinal fluid Wassermann was four plus. Routine blood and urine examinations were negative. Spinal fluid sugar was 50 mg. and spinal fluid pressure slightly increased. Basal metabolic rate was minus 9 per cent.

A sugar tolerance test showed low levels at four and six hours after the meal was given. He was recently found in a stuporous condition brought on by failure to eat a noon meal. While in this condition 1 c.c. of adrenalin was given hypodermically with slight benefit. Five minutes later 1½ c.c. of adrenalin were given by the intern and the patient was completely relieved. It is possible that these patients require larger doses of adrenalin than usual to elevate the blood sugar level. Pituitrin has had no effect.

For a period of several weeks in 1931 he was taking calcium lactate, fifteen grains, three times a day. During this time the frequency of attacks was materially lessened. In June 1932, the patient was placed on a high-fat low-carbohydrate diet with slight improvement. The attacks were less frequent but not abolished and occurred about two hours after breakfast. He was then placed on a more or less general diet with a carbohydrate feeding at midnight. This has effectively controlled his attacks and he has felt quite well. Sugar tolerance on 4/12/33 shows a nearly normal response.

The diagnosis is hyperinsulinism. The cause of the hyperinsulinism is unknown but is thought to be due to adenoma of the pancreas.

SUGAR CURVES, CASE I

After 100 gm. glucose, 6/20/32		After 1 c.c. adrenalin "H", 6/29/32	
Fasting,	100 mg. per 100 c.c.	Fasting,	42 mg. per 100 c.c.
½ hr.	158 mg. per 100 c.c.	½ hr.	46 mg. per 100 c.c
1 hr.	280 mg. per 100 c.c.	1 hr.	79 mg. per 100 c.c.
2 hr.	200 mg. per 100 c.c.	2 hr.	72 mg. per 100 c.c.
3 hr.	108 mg. per 100 c.c.	3 hr.	56 mg. per 100 c.c.
4 hr.	68 mg. per 100 c.c.	4 hr.	43 mg. per 100 c.c.
5 hr.	blood clotted.	5 hr.	blood clotted.
6 hr.	48 mg. per 100 c.c.	6 hr.	91 mg. per 100 c.c.

After 100 gm. glucose, 4/12/33

Fasting,	85 mg. per 100 c.c.
½ hr.	110 mg. per 100 c.c.
1½ hr.	165 mg. per 100 c.c.
2½ hr.	130 mg. per 100 c.c.
3½ hr.	90 mg. per 100 c.c.
4½ hr.	60 mg. per 100 c.c.
5½ hr.	93 mg. per 100 c.c.

CASE II

E. J., age 21, female. The patient was brought into the hospital 11/7/32 for a pelvic operation. She had been having convulsive seizures since the age of twelve.

They began with the onset of menstruation. There was only one attack the first year. Since that one, the attacks have gradually increased in frequency. Until the past two or three years they have occurred chiefly at menstruation. She now has attacks between menstruations but the most severe attacks are at menstruation. She may have many attacks in 24 hours or may have just one or two. Each attack begins with an aura of weakness, inability to concentrate, trembling and extreme nervousness. Sometimes she cries out just before loss of consciousness. This is shortly followed by loss of consciousness and generalized tonic and clonic convulsions. She has chewed her tongue very badly in some attacks. Foaming at the mouth is frequently noted. Following the convulsive seizure she is usually drowsy and sleeps for a short period. In between attacks she formerly felt quite well; during the past two or three years, however, she has been very nervous and restless, crying easily and feeling weak and tired most of the time. Excessive hunger is noted occasionally. She is unable to concentrate and feels that any attempt to read will bring on an attack. Mental confusion, amnesia, and some mental deterioration have been noted of late.

Physical and neurological examinations were essentially negative except for the absence of deep tendon reflexes.

Spinal fluid and blood Kahn tests were negative. Routine blood and urine examinations were negative. A roentgen-ray of the sella was negative. Spinal fluid sugar was 35 mg. Fasting blood sugar was 53 mg. Low sugar tolerance curves were obtained following a glucose meal. Before treatment was begun the adrenalin tolerance curve was flat. After treatment was instituted the adrenalin tolerance curve was considerably higher. Studies following three grains of luminal showed slight elevation of the sugar curve. Seale Harris [39] has also reported a slight rise of blood sugar following bromides.

SUGAR CURVES AFTER 1 C.C. ADRENALIN "H", CASE II

11/29/32		8/8/33	
Fasting,	53 mg. per 100 c.c.	Fasting,	75 mg. per 100 c.c.
½ hr.	70 mg. per 100 c.c.	15 min.	153 mg. per 100 c.c.
1 hr.	60 mg. per 100 c.c.	45 min.	145 mg. per 100 c.c.
2 hr.	54 mg. per 100 c.c.	1 hr.	111 mg. per 100 c.c.
3 hr.	52 mg. per 100 c.c.	2 hr.	117 mg. per 100 c.c.
4 hr.	44 mg. per 100 c.c.	3 hr.	100 mg. per 100 c.c.
5 hr.	48 mg. per 100 c.c.		
6 hr.	48 mg. per 100 c.c.		

SUGAR CURVES AFTER 100 GM. GLUCOSE, CASE II

11/8/32		11/18/32		3/6/33	
Fasting,	40 mg.	Fasting,	56 mg.	Fasting,	97 mg.
½ hr.	43 mg.	½ hr.	58 mg.	½ hr.	121 mg.
1 hr.	62 mg.	1 hr.	66 mg.	1 hr.	116 mg.
2 hr.	70 mg.	2 hr.	66 mg.	2 hr.	76 mg.
3 hr.	68 mg.	3 hr.	72 mg.	3 hr.	61 mg.
		4 hr.	60 mg.	4 hr.	69 mg.
		5 hr.	50 mg.	5 hr.	90 mg.
		6 hr.	50 mg.	6 hr.	89 mg.

SUGAR CURVES, CASE II

After 1 c.c. pituitrin "H", 3/20/33		After luminal, 3/22/33	
Fasting,	84 mg. per 100 c.c.	Fasting,	73 mg. per 100 c.c.
½ hr.	93 mg. per 100 c.c.	½ hr.	93 mg. per 100 c.c.
1 hr.	114 mg. per 100 c.c.	1 hr.	96 mg. per 100 c.c.
2 hr.	103 mg. per 100 c.c.	2 hr.	89 mg. per 100 c.c.
3 hr.	92 mg. per 100 c.c.		
4 hr.	86 mg. per 100 c.c.		

She was placed on a high-fat, low-carbohydrate diet with luminal. This resulted in complete cessation of attacks and of the symptoms noted between attacks. A pelvic operation was performed on 12/9/32: inspection and palpation of the pancreas at this time revealed nothing abnormal. Patient was kept on the same diet and on luminal following operation. At first three grains of luminal were required daily, later two, and finally one grain daily. However, if this one grain were not taken she would become very nervous, weak, etc., and would have occasional attacks. The addition to the diet of between-meal and midnight carbohydrate feedings did not permit further reduction of the luminal. However, with one grain of luminal daily and regular diet with extra carbohydrate feedings she has felt very well and has had no attacks.

She had been on various barbiturates before entering the hospital, with little effect on the epileptic seizures.

The diagnosis in this case was epilepsy and hyperinsulinism.

Case III

S. P., age 38, female. This patient first noted symptoms about one year ago (in January 1932). Whenever her meals are delayed, missed entirely, or are too light, she feels very weak, nervous and hot, and occasionally perspires freely. Trembling is quite marked at times, and numbness and tingling of extremities are very frequently noted. At times she cries very easily without any provocation. Headache has been a very marked symptom during the past year. Palpitation and tachycardia are occasionally noted. Drowsiness, stupor and nausea are also at times observed. Eating relieves these attacks. Excessive exertion may bring on an attack; she becomes fatigued very readily. One attack came on while she was driving her car and she had great difficulty in stopping the automobile. The attacks have been gradually increasing in frequency and she may have several a day. They are noted chiefly in the late afternoon or evening. They are more numerous and marked a few days before and on the first day of menstruation. Severe backache and pelvic pains are noted with menstruation. She usually has to go to bed the first day of menstruation and be given morphia for relief of pain.

Routine physical and laboratory examinations were negative. Basal metabolic rate was −22 per cent. Blood Wassermann was negative. Blood sugar during an attack was 85 mg. Symptoms were relieved by the administration of glucose. The first sugar tolerance test was done on 2/16/33, the first day of menstruation, and a blood sugar of 35 mg. at four hours was found. Two days later, 2/18/33, a normal sugar tolerance curve was obtained.

Sugar Curves after 100 Gm. Glucose, Case III

2/16/33		2/18/33	
Fasting,	88 mg. per 100 c.c.	Fasting,	88 mg. per 100 c.c.
½ hr.	130 mg. per 100 c.c.	½ hr.	109 mg. per 100 c.c.
1 hr.	71 mg. per 100 c.c.	1 hr.	114 mg. per 100 c.c.
2 hr.	49 mg. per 100 c.c.	2 hr.	121 mg. per 100 c.c.
3 hr.	47 mg. per 100 c.c.	3 hr.	133 mg. per 100 c.c.
4 hr.	35 mg. per 100 c.c.	4 hr.	148 mg. per 100 c.c.
5 hr.	—	5 hr.	104 mg. per 100 c.c.

Sugar Curves, Case III

After 1 c.c. adrenalin "H", 3/28/33		After 100 gm. glucose, 4/8/33	
Fasting,	109 mg. per 100 c.c.	Fasting,	108 mg. per 100 c.c.
½ hr.	181 mg. per 100 c.c.	½ hr.	144 mg. per 100 c.c.
1 hr.	170 mg. per 100 c.c.	1 hr.	86 mg. per 100 c.c.
2 hr.	133 mg. per 100 c.c.	2 hr.	82 mg. per 100 c.c.
3 hr.	103 mg. per 100 c.c.	3 hr.	92 mg. per 100 c.c.
4 hr.	92 mg. per 100 c.c.	4 hr.	93 mg. per 100 c.c.

The patient was placed on a high-fat, low-carbohydrate diet with no relief. Regular diet and extra carbohydrate feedings plus suprarenal extract have checked the attacks and resulted in considerable relief from menstrual discomfort. A sugar tolerance test on 4/8/33, the first day of the menstrual period, showed considerable improvement in sugar level.

Thyroid extract taken previously increased the basal rate to normal with relief of headaches but none of the other symptoms.

Case IV

S. G., age 37, female. For the past several years the patient had at times noted numbness in the right side of the head and lips, blurring of vision with spots in front of the eyes, and twitching of the lids. These symptoms were noted chiefly about one week before menstruation. Headaches, and weakness and nervousness were also noted at this time. During the past year these symptoms have increased; and weakness and fatigue have been so marked that she could not do much work. The attacks are accompanied by "craving for sweets" and are relieved by eating. Symptoms will return in one to two hours. Her associates have noted that the patient has been disoriented, forgetful, inattentive and restless during the first day of menstruation. She wanders about the room and aimlessly does various tasks. She talks constantly and frequently cries. She apparently does not understand what is being said to her.

Physical examination and routine blood and urine studies were negative. The fasting blood sugar during the first day of menstruation was 64 mg. Blood Wassermann was negative.

Sugar Curves, Case IV

After 100 gm. glucose, 3/27/33 (*Four days after onset of menstruation*)		After 1 c.c. adrenalin "H", 3/29/33	
Fasting,	103 mg. per 100 c.c.	Fasting,	88 mg. per 100 c.c.
½ hr.	131 mg. per 100 c.c.	½ hr.	107 mg. per 100 c.c.
1 hr.	109 mg. per 100 c.c.	1 hr.	119 mg. per 100 c.c.
2 hr.	108 mg. per 100 c.c.	2 hr.	86 mg. per 100 c.c.
3 hr.	86 mg. per 100 c.c.	3 hr.	82 mg. per 100 c.c.
4 hr.	66 mg. per 100 c.c.	4 hr.	40 mg. per 100 c.c.
		5 hr.	50 mg. per 100 c.c.

This patient was placed on a high-fat, low-carbohydrate diet, plus extra carbohydrate feedings, the day before and the first day of menstruation. In addition to this, suprarenal extract was also given. This régime has resulted in complete relief of symptoms and she has now passed through three normal menstrual periods.

Conclusions

1. Spontaneous hypoglycemia may be secondary to any disturbance of the blood sugar regulatory mechanism, but it is frequently secondary to hyperfunction of the pancreatic islets following hyperplasia or tumor growth or simple functional changes.

2. It is possible that some relief of menstrual pains, weakness and nervousness, will result from treatment directed toward increasing the blood sugar.

3. All epileptics should have blood sugar studies, as there seems to be a small number whose convulsions are secondary to hypoglycemia.

4. Medical treatment consists chiefly in dietary régime to prevent lowering of the blood sugar level.

5. If medical treatment is unsuccessful, surgery should be resorted to. If no tumor is found, resection of more than half of the pancreas is justified. Apparently too small a portion of the pancreas has been removed in previous cases.

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PNEUMOCOCCIC MENINGITIS: RECOVERY WITH FELTON'S SERUM *

By WILLIAM S. REVENO, M.D., and NELSON MCLAUGHLIN, M.D.,
Detroit, Michigan

PNEUMOCOCCIC MENINGITIS is generally considered as offering little or no hope of recovery. The evidence in this respect presented by Kolmer,[1] by Schottmüller and by many others, is anything but encouraging to the physician called upon to treat this fulminating disease.

A slowly growing list of recoveries is, however, being gradually recorded, and, while the number is still pitifully small, it constitutes concrete evidence that a totally pessimistic attitude is unwarranted. The successful results have been obtained through a variety of therapeutic procedures, namely: (1) intrathecal and intravenous serum injections; (2) repeated lumbar and cisternal punctures, alone or combined; (3) the use of ethyl hydrocuprein hydrochloride; (4) potassium permanganate instillations by the technic of Nott; and (5) spontaneous recovery.

Robertson [2] believes that treatment has most chance of success in cases due to Type I pneumococcus infections since it is against this type that the most potent immune serum has been produced. Harkavy [3] cites a case of meningitis secondary to an otitis media which was found to be due to a Type I pneumococcus and recovered after treatment with Felton's serum. The cases reported by Rohrbach,[4] Ervine, Cummings,[5] Apfel,[6] Lynch,[7] Simpson,[8] Shuller,[9] and Croft [10] were all treated with antipneumococcic sera. Those of Uhr,[11] Globus and Kasanin,[12] and Amesse [13] were subjected to repeated lumbar and cisternal punctures, alone or combined. Carbonell and Cook [14] and Ratnoff and Litvak [15] each report a case treated with a mixture of ethyl hydrocuprein hydrochloride and antipneumococcic serum, while Weinberg [16] used potassium permanganate solution by the Nott technic.

The experimental work of Stewart [17] and of Kolmer [18] has shed considerable light on the nature of the process in pneumococcic invasion of the subarachnoid space. Each has recommended a method of treatment based on his experimental results. Stewart treated Type I pneumococcic infections in dogs by the quadruple method of injecting mixtures of antipneumococcic serum and optochin (ethyl hydrocuprein hydrochloride) into the cerebral subarachnoid space (both sides), the cisterna magna, and the lumbar region of the cord. He used a mixture of 15 c.c. Type I serum with 0.75 c.c. of 1 per cent optochin, and found that if there were no obstruction to drainage, and if the drug did not unfavorably affect the respiratory

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From the Highland Park General Hospital, Highland Park, Michigan.
Stock Felton's antipneumococcic serum furnished through the courtesy of Parke, Davis and Co.

center, progressive sterilization of the meninges, with some recoveries, could be produced.

Kolmer found it difficult to duplicate this treatment in human beings because here treatment is frequently delayed to the point at which the subarachnoid fluid is extremely purulent and accompanied by plastic exudate. He recommends the use of antipneumococcus serum to every 25 c.c. of which has been added 1 c.c. of 1 per cent optochin solution. Felton's serum is preferable because of its high content of antibodies. Kolmer advised that the serum-optochin mixture be injected into the cisternal space, after drainage, and that it also be injected into the carotid arteries.

Case Report

A. S., white female, age 20, fell while dancing December 31, 1932, striking her head on the floor. A slight swelling appeared on the left forehead but no other signs developed until the afternoon of the following day (January 1, 1933) when she complained of a severe headache.

Her past history was irrelevant except for frontal and maxillary sinusitis in the winter and spring of 1931–1932.

She was first seen January 2, 1933 by one of us (N. McL.). Her temperature was 101°. The headache was persistent; there was tenderness over the right maxillary antrum and ethmoid area, and the right ear drum appeared to be bulging. The following day (January 3) the temperature was unchanged, the headache was of increased severity, and she complained of some disturbance in vision. The condition continued unchanged until the evening of January 5 when she had two severe chills and became increasingly stuporous. On the morning of January 6 the tenderness noted before over the right maxillary antrum and ethmoid region had shifted to the left side and there was a noticeable bulging of the left eyeball. Examination for evidence of sinus involvement was made at this time by Dr. J. W. Croushore and none was found. The patient continued to develop increased visual disturbance, stupor, and headache. Her temperature mounted to 102°. Vomiting developed. She was transferred to the hospital January 7, 1933.

Examination on admission showed a well developed young white female, somewhat disoriented and stuporous, whose temperature was 103.4° and pulse 70. The blood pressure was 130 systolic and 80 diastolic. There was a marked bulging of the left eye, a choking of the inner half of the left optic disc, slight nasal congestion, rigidity of the neck and back, sluggish knee reflexes, a negative Babinski and a positive Kernig sign.

These findings, together with the history, warranted a diagnosis of meningitis. Spinal puncture was performed. There was no increased pressure and the fluid was slightly opalescent. The laboratory findings are recorded in table 1.

She was given 25 c.c. of 50 per cent glucose solution intravenously every six hours, and an additional effort was made to reduce cerebral pressure by means of rectal instillations of 33 per cent magnesium sulphate solution.

January 8: Patient was somewhat brighter. Temperature 102°, pulse 74. The physical findings were unchanged. The headache was still severe. The rectal instillations of magnesium sulphate were discontinued. Chloral hydrate in 15 grain doses was given for restlessness. Intravenous injections of 25 c.c. of 50 per cent glucose solution every six hours were continued, and a 5 c.c. ampule of 5 per cent Uritone solution was given intravenously every four hours. By late afternoon she was irrational, there was slight cyanosis, the temperature was 104.4°, and the pulse 96. There was a slight bloody discharge from her nose containing an occasional clot of blood.

TABLE I

Laboratory Findings

	Cerebrospinal Fluid						Blood Count					
	Cell Count	Globulin	Smear	Sugar	Gold Curve	Culture	Total White Cells	Filament	Non-Filament	Small Lymphocyte	Endothelials	Treatment
Jan. 7	3530	4+	Not made	−	0002333300	Bile soluble encapsulated diplococci (Pneumococci Types I and II)	12700	49%	26%	22%	3%	Symptomatic
Jan. 9	4860	4+	Polynuclears and pneumococci	−		"	13900	48	24	24	4	30000 units Felton's serum (intravenously)
Jan. 10	1400	2+	"	−		"	23300	58	30	8	4	10000 units intravenously 10000 units intraspinally
Jan. 11							12900	55	19	21	5	10000 units intravenously
Jan. 12	5800	3+	"	−		"	25400	56	28	8	8	20000 units intravenously
Jan. 13	950 (Cistern fluid)	3+	"	−		"	20000	54	30	10	6	20000 units intracisternally
Jan. 14	Not counted	4+	"	−		"	17500	60	25	12	3	10000 units intravenously
Jan. 15	2320	4+	"	−		"						10000 units intravenously
Jan. 16	320 (Cistern fluid)	2+	"	.061 gm.		"	15500	66	18	13	1	No serum
Jan. 17							15200	67	17	16	0	" "
Jan. 18	1150	3+	Polynuclears—No organisms	+	0012332100	No growth	14500	62	18	18	2	" "
Jan. 19	870	2+	"	.058 gm.		Pneumococci	11000	67	14	18	1	" "
Jan. 20							13000	63	16	20	1	" "
Jan. 21							13400	60	16	22	2	" "
Jan. 22												" "
Jan. 23	860	2+	Polynuclears—No organisms	.048 gm.		Occasional pneumococci	12500	57	15	26	2	" "
Jan. 24							11000	57	15	25	3	" "
Jan. 25							14000	57	16	25	2	" "
Jan. 26							12500	60	15	22	3	" "
Jan. 27	90	4+	Polynuclears and pneumococci	.070 gm.		Occasional pneumococci	11500	60	15	23	2	" "
Jan. 28							9800	58	14	25	3	" "
Jan. 30							9500	58	14	26	2	" "
Jan. 31							10000	60	16	22	3	" "
Feb. 1	50	4+	Polynuclears—No organisms	.065 gm.	1222334321	No growth	9200	60	15	22	3	" "
Feb. 3							10000	60	13	23	4	" "
Feb. 4	40	2+	Few polynuclears No organisms	.062 gm.		No growth						

Blood culture Jan. 7 and Jan. 9 showed no growth.

This epistaxis became more marked during the night so that it was necessary to pack the nose.

January 9: Temperature 101.8°, pulse 72. The headache was severe, and the patient was somewhat irrational. Her left eye was still prominent and slight internal strabismus was noted. Rigidity of the neck was marked. The abdominal reflexes were hyperactive, the knee reflexes sluggish, the Kernig sign was positive and the Babinski negative.

Spinal puncture showed the fluid cloudy and under increased pressure (34 mm. mercury). There was no evidence of subarachnoid block. Twenty cubic centimeters were withdrawn. The culture of the spinal fluid withdrawn on January 7 showed pneumococci. On typing, these were found to agglutinate with Type I and II sera.

The use of Felton's antipneumococcic serum was believed indicated, and after preliminary tests for serum sensitivity, 10,000 units were given intravenously at 11 a.m., 3:30 p.m., and 7:45 p.m. All other treatment was discontinued.

January 10: Temperature 101.2°, pulse 82. The patient's condition was essentially unchanged. The internal strabismus of the left eye was more marked. Edema of the nasal portion of left optic disc was still pronounced. Spinal tap showed cloudy fluid under increased pressure. Queckenstedt's sign was negative. Ten thousand units of Felton's serum were instilled intraspinally by gravity. At 2:30 p.m. 10,000 units of Felton's serum were given intravenously. She felt somewhat improved late that afternoon but by evening she was quite irrational. A drawing downward of the right corner of the mouth was noted.

January 11: During the night difficulty in swallowing developed. At 4:30 a.m. the temperature was down to 99.8° and the pulse 80. Her condition seemed improved in the morning. The headache was better. Strabismus of the left eye was still marked. Right facial paralysis with inability to purse the lips and contract the orbicularis oculi muscle was quite pronounced. She was given 10,000 units of serum intravenously. In the afternoon she began to complain of more headache. The temperature rose to 103° but the pulse for the first time was up to 108.

January 12: Patient had urinary retention during the night and required catheterization in the morning.

Temperature 102.4°, pulse 100. Blood pressure 124/74.

Spinal puncture was performed: the pressure was up to 30 mm. mercury. Queckenstedt's sign was negative. Fifteen cubic centimeters of cloudy fluid were withdrawn (pressure reduced to 8 mm.). Ten thousand units of Felton's serum were given intravenously at 10 a.m. and again at 6 p.m.

January 13: Comfortable night. Temperature 101.4°, pulse 88.

Cisterna puncture was performed and 20 c.c. of cloudy fluid withdrawn and 20,000 units of Felton's serum instilled. This was followed by dyspnea which was relieved by seven minims of adrenalin hydrochloride (1–1000) and ¼ gr. of morphine.

January 14: Temperature 99.8°, pulse 100. Spinal puncture was performed and 20 c.c. of cloudy, thick, yellowish, rapidly coagulating fluid were withdrawn. Queckenstedt's sign was negative. The cell count could not be done. Ten thousand units of Felton's serum were given intravenously immediately following the spinal tap. The patient had a comfortable day.

January 15: Temperature 100.2°, pulse 100. Definite general improvement was noted. The headache was practically gone. Soreness and stiffness of the neck and back were still marked. The strabismus of the left eye and protrusion of the eyeball were practically completely gone. The edema of the left optic disc had cleared. The abdominal reflexes were hyperactive, the knee reflexes sluggish, and the Babinski negative. Kernig's sign was negative on the left but positive on the right.

Spinal puncture performed: pressure not increased; Queckenstedt's sign negative; fluid yellow and opalescent. Ten thousand units of Felton's serum were given intravenously.

January 16: Temperature 99.8°, pulse 92. The patient was very comfortable. The reflexes showed the same responses as on the previous day.

Spinal tap was attempted both in the fourth and third lumbar interspaces but was unsuccessful. Cisterna puncture was performed and 25 c.c. of clear fluid withdrawn. Because of the freedom from symptoms, and in view of the cisterna fluid findings and the drop in the non-filament percentage from 25 to 18 (table 1), no serum was given. From this day on, the non-filament percentage of polynuclear cells, in addition to the cerebrospinal fluid findings, was used as a guide in deciding the necessity for further serum treatment.

January 17: Temperature 101.8°, pulse 110. A slight increase in the activity of the knee reflexes was noted. The right Kernig was only slightly positive. Slight improvement in the right facial paralysis was observed. The patient's condition seemed satisfactory and she was quite comfortable. No spinal tap was performed and no serum given.

January 18: Temperature 99.6°. The patient had a very comfortable day. The knee reflexes were active, the Kernig sign negative. The facial paralysis was unchanged.

Spinal puncture showed opalescent fluid under normal pressure. Queckenstedt's sign was negative. No serum was given.

January 19: During the night the temperature rose to 103°. In the morning the patient showed an urticarial rash over the legs, thighs, arms and chest. For the first time there was noted a paralysis of the external rectus muscle of the right eye with inability to move the eyeball laterally beyond the midline.

Spinal tap showed an opalescent fluid under no increased pressure.

January 20 and 21: Condition remained unchanged. The urticaria began to clear up but joint pains were quite marked. Salicylates were administered.

January 22: The patient developed a mild coryza and occipital headache. Her condition was otherwise good.

January 23: The patient's condition was satisfactory although there was still a slight temperature rise. The abdominal reflexes were normal as were the knee reflexes. The Kernig and Babinski signs were negative. The right facial paralysis showed slight improvement but the abducens paralysis remained unchanged.

Spinal tap showed turbid fluid under no increased pressure.

January 24, 25, 26: The patient's condition showed steady improvement.

January 27: Facial and abducens paralysis improved. Spinal fluid clear, yellowish, and under normal pressure.

January 28, 29, 30, 31: Condition good. Facial and abducens paralysis improving slowly.

February 1: Condition good. Spinal fluid clear, pressure not increased.

February 4: Spinal fluid clear. Pressure not increased.

She was discharged from the hospital on February 5, 1933. Her physical condition was good. The facial paralysis was clearing rapidly but the right abducens paralysis was improving only very slowly.

By April 1 her facial paralysis had cleared up completely. The right abducens paralysis also showed evidence of improvement, but this was not progressing as rapidly.

Eye examination by Dr. Parker Heath on April 4, 1933 showed vision 5/6 in both eyes; measurement of muscle balance showed 14 degrees esophoria for distance and the same in accommodation.

The ophthalmoscopic examination showed some loss of transparency along the course of the vessels, otherwise the findings were normal.

Visual field studies showed nothing significant. There were no scotomata and the blind spots were normal. There was residual squint in the right eye.

On April 3, 1933 stereoscopic roentgen-ray studies were made of the skull by

Dr. Edward G. Minor. There was no evidence of any definite sinus pathology nor of any recent or old fracture.

SUMMARY

1. A patient with pneumococcic meningitis (probable portal of entry the paranasal sinuses), with the infecting organism pneumococcus Type I and II, was successfully treated by intravenous, intraspinal and intracisternal instillations of 120,000 units of Felton's anti-pneumococcic serum.

2. Recovery set in after seven days of treatment and was evidenced not only by clinical improvement but by a reappearance of sugar in the cerebrospinal fluid, a lowering of its cell count, and a drop in the percentage of non-filament cells in the blood smear. This latter finding, namely the non-filament percentage,[19] was relied upon as a gauge of the activity of the infection. As long as this figure remained between 8 and 16 it was felt that the infectious process was under adequate control.

3. As a residuum of the disease, the patient had a right facial and a right abducens paralysis. The former developed on the fourth day and the latter on the day after admission to the hospital. The facial involvement cleared rapidly but the sixth nerve paralysis took fully two months longer for recovery.

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CHICAGO AS A MEDICAL CENTER

FROM a mere stockade with two blockhouses established as Fort Dearborn in 1803 by the United States Government, Chicago has had a noteworthy development. The many phases of Chicago's phenomenal growth from an insignificant hamlet of log houses to a metropolitan center of great importance were dramatically portrayed at A Century of Progress from June to November of 1933.

Of all the exhibits at the World's Fair, none drew more close observation and widespread acclaim than those dealing with medicine, surgery, and the basic and allied sciences, most of which were located in the Hall of Science. In concise form these exhibits showed the lay public what medicine has accomplished during the last 100 years, and how Chicago has contributed to that development.

While the purpose of this article is to call the attention of physicians to the Chicago of today as a medical center, a brief word as to the development of medicine in Chicago may be in place.

Medical Schools. Early medical needs were met by the Army surgeons and a few pioneer general practitioners. An important step was taken when in 1837 Daniel Brainard, a cultured, well educated man—he had studied in Paris—who was already a leading surgeon in the Northwest, founded Rush Medical College. Dr. Brainard gathered about him a notable group of men and from 1837 to the present time Rush Medical has been a prominent school in Chicago and the Northwest. Its long association with the Presbyterian Hospital and the Central Free Dispensary and its affiliation and later union with the University of Chicago, its voluntary raising of standards, its four year course, its compulsory fifth year are among the epochs in its history and help explain its leadership in medicine, its production of notable practitioners and specialists of many types and its contributions to medical science and literature.

In Dr. Brainard's faculty for several years was a young man, N. S. Davis. It has well been said that two men of the type of Daniel Brainard and N. S. Davis, each determined to lead and unable to follow, could not be members of the same faculty. So N. S. Davis, taking with him such men as William H. Byford, H. A. Johnson and Daniel Rutter, left Rush Medical College and founded the Chicago Medical College. This school was to demand higher entrance requirements and to have a graded course. Whether Dr. Brainard did not believe in the principle of these changes or in the feasibility of putting them into practice at that time is not quite clear, but Dr. Davis did believe in the principle and did put them into practice. Later all colleges followed his lead. From its first course in 1859 to the present, the Chicago Medical College has had a career of progress and today, as Northwestern University Medical School with magnificent labora-

tory and clinical buildings, a superior faculty and an enthusiastic student body, it is well known in the medical field.

The College of Physicians and Surgeons, a proprietary medical school, was started in 1881, depending largely on the nearby Cook County Hospital for its clinical advantages. It had many outstanding didactic and laboratory teachers and did good work. In 1897 it became the Medical Department of the University of Illinois. It still has the advantage of being located in "the medical center of the west side," close to the Cook County Hospital, but it now has splendid modern buildings of its own, embracing

FIG. 1. Rush Medical College.

hospitals, research departments, out-patient department and library. It is a university of which the state is justly proud.

Many small second or third rate medical schools sprang up in Chicago in the last 30 or 40 years of the nineteenth century. Several of these died a natural death. Others were given a lethal potion by the American Medical Association through its Council on Medical Education. Several schools were gathered into the Medical Department of Loyola University. This latter institution immediately began re-arranging, improving the physical plants, unifying work, raising standards, until today it is a Class A school

in high favor, with a good faculty and a worthy group of teaching hospitals under its control—Mercy, Misericordia, St. Anne's, St. Bernard's, St. Elizabeth, St. Mary of Nazareth, John B. Murphy, Alexian Brothers, Lewis Memorial and Oak Park.

Following out the plan of President William R. Harper, the University of Chicago for some years confined its medical course to the work given in the Departments of Anatomy, Pharmacology, Pathology, Bacteriology, Physiology and Chemistry. For the last few years, however, it has given a full four year medical course on the University campus. A fine group

FIG. 2. Montgomery Ward Memorial Building of Northwestern University Medical School, with Passavant Hospital in the background.

of buildings was erected, largely through the efforts of Dr. Frank Billings. While research is stressed, undergraduate teaching is also carried out. The students at the end of the first two years choose whether they will remain at the University on the south side to continue work or will go to the west side to Rush Medical College. All students on finishing their four years are eligible for the degree of doctor of medicine conferred by the University of Chicago.

To these different medical schools and to their hospitals, laboratories, research departments and wards, the College of Physicians will be invited to demonstrations and clinical conferences that will surely be informing and

stimulating. It will also be of interest to many members to see the physical plants of some of the departments, and the equipment, and to learn the methods of teaching and investigation that are there in vogue.

Hospitals. There are in Chicago more than 100 hospitals. Of these, in 1933, 62 were on the approved list of the American College of Surgeons. Discussion of these hospitals will be confined to those which will participate most actively in the meeting of the American College of Physicians.

Cook County Hospital is a tax-supported institution maintained for the medical and surgical treatment of the indigent poor. It was founded on March 30, 1847. The City Hospital, opened in 1856, was purchased

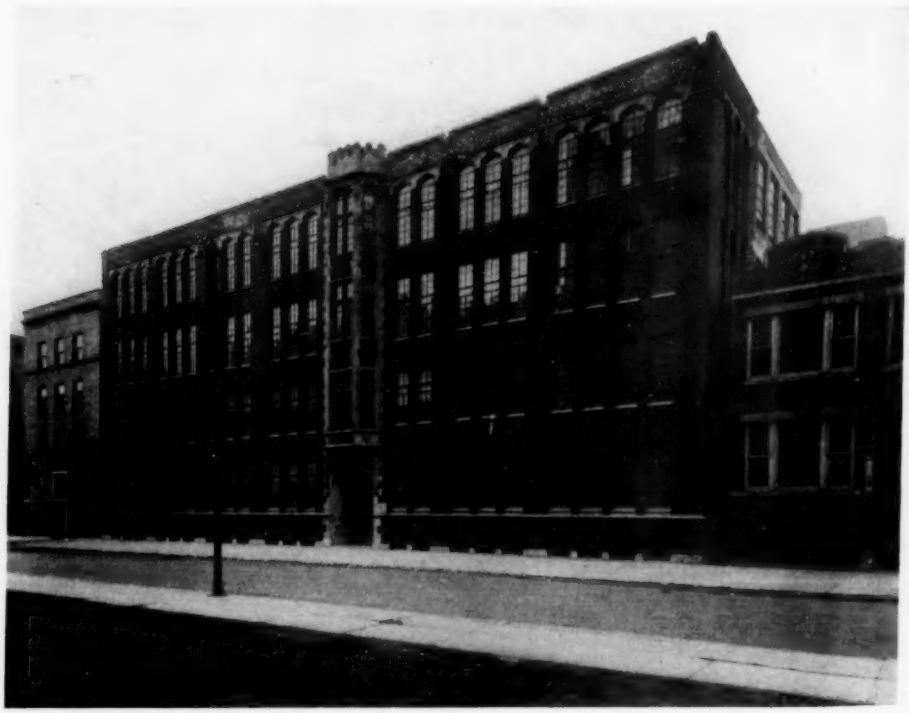

FIG. 3. Loyola University School of Medicine.

by Cook County in 1866. Between the years 1863 and 1865 it had been used as a United States military hospital.

In figure 4 are shown the seven buildings comprising the Cook County Hospital which is situated in the medical center of Chicago. The divisions of Cook County Hospital are: general, children, psychopathic, laboratory, tuberculosis, men's medical, and contagious. The hospital has a capacity of 3300 beds. The attending staff consists of 130 physicians who serve for a period of six years and are under Civil Service. There are 93 interns at present who serve an internship of 18 months each. In addition there are 33 residents.

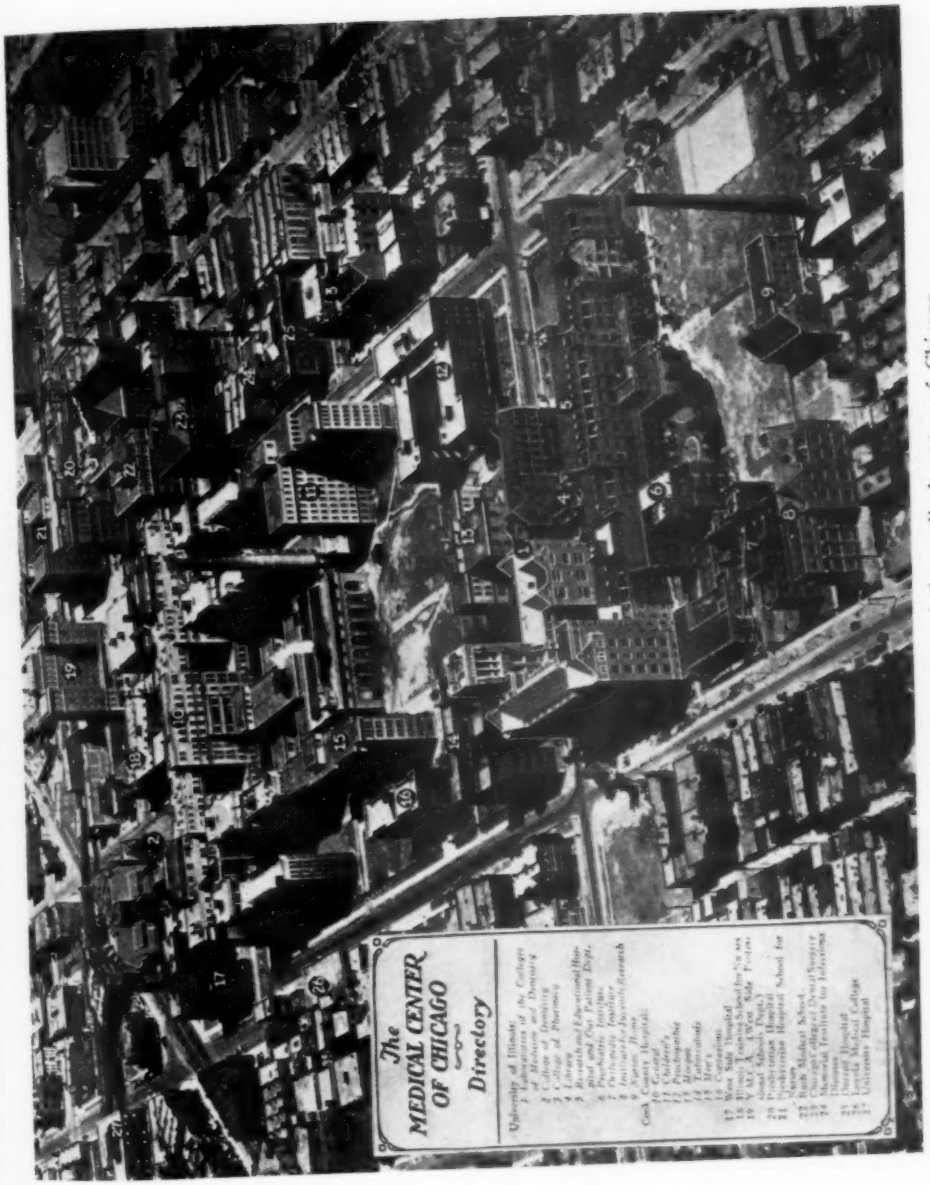

FIG. 4. Airplane view of the medical center of Chicago.

It is impossible to estimate the enormous influence the County Hospital has had on the medical work of Chicago. Though often harmfully enmeshed in politics, though at times operating in an atmosphere of extravagance, mismanagement and graft, it has gone ahead caring for—and in general well caring for—an increasing number of the indigent sick through its attending and intern staff. The positions on each one of these staffs have always been coveted, not so much for the prestige attached to them as for the opportunity to increase clinical experience. The roll of the names on the attending staff includes along with forgotten political appointees a goodly proportion of the city's leading physicians, surgeons and specialists, with many teachers of outstanding ability. The list of ex-interns, whose appointment for years has been on the basis of competitive examination, is an impressive one, including names well known not only in Chicago and the United States but often abroad as well. In this list—we omit the names of those still living—we find among others Nicholas Senn, William E. Quine, E. Fletcher Ingals, Roswell Park, William T. Belfield, John B. Murphy, Frank Billings, John A. Fordyce, S. P. Black, Weller Van Hook, A. E. Halstead, Adolph Gehrmann, H. T. Ricketts, and Theodore Tieken.

There has always been carried out in Cook County Hospital some type of undergraduate instruction in amphitheater, morgue, ward or laboratory. This is true today. A recent development is the organization, not for profit, of the Cook County Graduate School of Medicine. Started in 1932, this school will, through the hospital staff, utilize the wealth of facilities afforded by the hospital. Short courses of a few weeks or longer ones of a year will be offered in clinics, wards, laboratories of various kinds, the out-patient department, morgue, etc. The fact that in the first year of its existence 250 physicians were enrolled seems to indicate that the school is meeting a demand and that it bids fair to prosper.

Another public institution deserving of mention is the Municipal Tuberculosis Sanitarium. This was opened in 1915 and is a specialized hospital with services for all stages of pulmonary tuberculosis. It has a capacity of 1246 beds. Its wards are open for teaching to the various medical schools of the county.

Mercy Hospital (figure 5) is one of the oldest hospitals in Chicago, having been started in 1849 as the Illinois General Hospital of the Lakes. Under the management of the Sisters of Mercy it has grown to be a general hospital of 365 beds, caring for all types of disease except contagious. Its institute of radiation therapy, containing some of the finest roentgen-ray facilities in the United States, places Mercy in a position to treat any type of tumor or malignant disease. Its ample teaching facilities are utilized by Loyola University with which it is intimately related. Without disparagement of others, one may say there are three names which by common consent are associated with the development of Mercy Hospital, N. S. Davis, Sister Raphael, and John B. Murphy. Each one of these gave years of devoted

service to the upbuilding of the institution to the end that it might better take care of patients and spread medical knowledge through instruction in its wards and amphitheaters.

Plans for St. Luke's Hospital were consummated during the Civil War. A hospital to care for the sick soldiers of Camp Douglas was very much needed. As a result a frame building with a seven bed capacity was opened in 1864. Today St. Luke's—by the way the tallest hospital in the world—has a bed capacity of 659 with investment in land, buildings and equipment of more than $5,000,000. On its staff are many of the leading practitioners of Chicago. Its intern service is eagerly sought. Small clinics and ward clinics are open to undergraduates. Excellent work has been and is being

FIG. 5. Mercy Hospital.

done in roentgen-ray, pathological and other laboratories. The school of nursing is of highest rank.

Michael Reese Hospital grew out of the first Jewish hospital established in Chicago, in 1868. This hospital was destroyed by the fire of 1871. Michael Reese, who died in 1873, left through his will a fund sufficient to erect a new building. The United Hebrew Charities of Chicago founded the institution, named it in honor of Michael Reese and made it non-sectarian. In the last few years, largely through special funds given by various donors, there has been a remarkable development of research work at Michael Reese, and various interesting clinical and laboratory investigations are now being carried on. Among the special departments of the hospital may be mentioned the cancer clinic, the radium therapy, electro-

therapy and cardiac departments, the prenatal station and the department of pediatrics. The out-patient department, social service department and nursing school are all of high grade.

Passavant Memorial Hospital (figure 2) was established in 1865, being at that time called the Deaconess Hospital. It was located in a frame residence with a capacity of only 15 beds. When the founder, the Rev. William A. Passavant, died in 1894 the name was changed. In 1926 the new Passavant Memorial Hospital was constructed on the downtown campus of Northwestern University. It has a capacity of about 250 beds; and its equipment for the treatment of patients is of the most modern type. It is

FIG. 6. St. Luke's Hospital.

controlled in its medical management by Northwestern University and is well utilized as a teaching and research hospital by that University.

It may be mentioned here that Wesley Hospital, founded in 1888 and a beneficiary of funds left by William Deering, is another hospital affiliated with Northwestern University. Its wards are used for teaching. It is planned that ultimately it will be on the same campus with Northwestern University Medical School.

Presbyterian Hospital was founded in 1883 by Dr. Joseph P. Ross, a member of the faculty of Rush Medical College, largely because he felt the need of a teaching hospital to care for the clinic patients of Rush. From a small beginning it has gradually enlarged until now it has 439 beds and, together with the building of Rush Medical College, occupies an entire block.

Its close association with the College, which controls its staff appointments, and with the Central Free Dispensary, and of late its affiliation with the University of Chicago have made it a center of teaching and research. Its wards are open to undergraduate students. Its training school is justly famed.

The Research and Educational Hospitals (figure 9) had their origin on July 5, 1919 when the State Department of Public Welfare and the State University agreed upon a plan for constructing and maintaining a group of hospitals, laboratories, library and allied institutions in the medical center of Chicago on the West Side. Their aim was to provide medical treatment for

FIG. 7. Michael Reese Hospital.

the indigent sick of the state, to educate practitioners in the prevention as well as the cure of disease and to foster research. Not all the hospitals and laboratories planned have been constructed, but a splendid beginning has been made. The clinical building for the medical department has been put up. In September 1924 the out-patient department of the Research and Educational Hospitals was established. The general hospital was opened in 1925. The Surgical Institute for Children was opened in the spring of 1930, and in 1931 the Psychiatric Institute started receiving patients.

The University of Chicago Clinics comprise a group of hospital and medical buildings situated for the most part on the University campus. The English Gothic style which is characteristic of all the University buildings

has been carried out very successfully in the architecture of the medical group. In addition to the service rendered to the public by the care of a large number of patients, the purpose of the clinics is to afford exceptional opportunities to students of medicine who are preparing for a career as practitioners, teachers or investigators. In all departments stress is laid upon research, and valuable studies are everywhere in progress.

The Albert Merritt Billings Hospital, a unit of the University of Chicago Clinic, was opened in 1927 as a general hospital and has also been used for gynecology and orthopedic surgery. It includes an out-patient department, the Max Epstein Clinic. The pediatric department is housed in the Bobs Roberts Memorial Hospital for Children. The Nancy Adele McElwee Memorial and the Gertrude Dunn Hicks Memorial, together with the

FIG. 8. Presbyterian Hospital.

country home for convalescent children at Prince Crossing, in part owned by the University and in part controlled by them, offer unusual opportunities for the care and study of orthopedics as related to children.

The Chicago Lying-In Hospital and Dispensary was founded in 1895 in four rooms located in a poverty stricken neighborhood. Today it has a modern hospital with a capacity of 260 beds. It is an outgrowth of years of intensive effort on the part of Dr. Joseph B. DeLee and a group of devoted supporters. The Dispensary on Maxwell Street gives treatment annually to more than 3,000 women during confinement in their homes. It is a teaching institution, being attended yearly by about 250 students of universities of the central states and nurses from 16 affiliated schools of nursing. The Chicago Lying-In Hospital and Dispensary is independently owned but became a unit of the University of Chicago Clinics in 1926.

Also affiliated with the University of Chicago, though not on its campus, is the Children's Memorial Hospital. This was founded in 1884 by Mrs. Julia F. Porter in memory of her son. It was reorganized in 1903 and its present name given to it. It is well known as a hospital in which excellent care is given to children not over the age of 13, and in which much investigative work of importance in medicine, surgery and the specialties has been carried on.

Under the guidance of the University of Chicago is Provident Hospital, founded in 1891 by a group of public spirited men of Chicago. Recently the hospital has moved into its new quarters and today is one of the most modern and outstanding negro hospitals in the world. It furnishes excellent opportunities not only for the care of negro patients, but for the training of colored interns and physicians.

Medical Societies. Chicago deserves consideration as a medical center because of the number of medical societies and famous medical organizations which have established their headquarters in that city.

At the head of these in importance and influence is the American Medical Association, the largest medical association in the world, with headquarters at 535 N. Dearborn Street. It was founded in Philadelphia in May 1847. The nature of the American Medical Association, its growth and its objects are so familiar to physicians as to need little comment. The names of two Chicago men come to mind in connection with the work of the Association, one that of N. S. Davis, the founder, and the other that of George H. Simmons, for many years its secretary, whose genius guided the Association in its marvelous development.

To many doctors the various councils and bureaus and special departments are but names. If visitors from the College of Physicians will but go to the American Medical Association headquarters and see the well organized, smoothly running activities of these various groups, they will be convinced of the magnitude of the undertaking and the efficiency with which the work is done. They will have renewed pride in our great American Medical Association.

Several noteworthy journals are published by the Association. In addition to the *Journal of the American Medical Association,* which was established in 1883 and is the leading medical journal in the United States and has the largest circulation of any medical journal in the world, the Association publishes the well known series of "Archives" of various specialties, and the *American Journal of Diseases of Children.* It also publishes the *Quarterly Cumulative Index Medicus,* the *American Medical Directory* and *Hygeia.*

The American Hospital Association, a charitable and educational association of hospitals and hospital people, is located in Chicago at 18 E. Division Street. Organized in Cleveland in 1899 with a membership of nine people, it has grown until now it numbers 1,533 institutions in the United States and Canada, and 2,646 leading administrators, members of

FIG. 9. Research and Educational Hospital group and University of Illinois College of Medicine.

FIG. 10. University of Chicago Clinics.

boards of trustees and of medical and nursing staffs, and heads of departments. During the 35 years of its history the Association has spent more than a million dollars in the development of those principles and practices which have in a very large way assisted more than 7,000 institutions.

The American College of Surgeons with headquarters at 40 E. Erie Street has at the present time 11,214 Fellows, who are practicing surgery in North and South America. For 16 years the American College of Surgeons has conducted as one of its important activities the hospital standardization movement. It has spent in the neighborhood of one million dollars in making thousands of individual surveys of hospitals. As a

FIG. 11. American Medical Association.

result it has been a powerful influence in eliminating commercial and unscientific features from many hospitals in this country. The standards of these institutions have been distinctly raised, and the care of the sick and the training of the staff and of undergraduates have been definitely improved. The College sponsors a number of other important activities. We mention the library and department of literary research which provide physicians with abstracts, bibliographies, package libraries, etc. There is also a department of clinical research which is investigating such subjects as bone sarcoma, the treatment of malignant disease, and the treatment of fractures.

We should mention also *Surgery, Gynecology and Obstetrics*, the official publication of the American College of Surgeons. This monthly journal

was started in 1905, edited by "active surgeons for active surgeons," and today is recognized as one of the leading surgical publications of the world.

There are many medical societies. Nearly all the specialties are represented by local societies. The parent society of all, the Chicago Medical Society, has been in existence since 1850. At the present time there is a central body known as the Chicago Medical Society, with a membership which is considered to be the largest in the world. Scientific meetings are held each week. Then there are 15 branches of this central body, each branch selecting its own officers and holding scientific meetings once a month. The Chicago Medical Society coöperates with the State Society in various ways, as for instance through its Educational Committee, whose headquarters are in Chicago. The *Illinois Medical Journal*, a monthly magazine, the official journal of the organization, is published in Chicago.

FIG. 12. American College of Surgeons group, showing main building (left); John B. Murphy Memorial (center); and Surgery, Gynecology, and Obstetrics building (right).

The Institute of Medicine of Chicago has been in existence for some 15 years. It is modeled after the College of Physicians of Philadelphia, the New York Academy of Medicine and similar organizations. Its membership of about 400 is carefully selected. It sponsors and encourages high grade practice of medicine, investigation in medicine and related sciences, and medical features that are of interest to the public. Though comparatively young, its activities have already been productive of great good.

The visiting members of the American College of Physicians and their wives will find many interesting features in Chicago aside from its medical landmarks. A more detailed description of these will be given in a folder which is to be issued at the time of the meeting. We may mention here, however, the Adler Planetarium and Astronomical Museum, the Art Insti-

tute, the Chicago Historical Society, the Chicago Museum of Natural History, The Field Museum, the Shedd Aquarium, the Museum of Science and Industry, The Oriental Institute, to say nothing of the Stock Yards, the great mail order houses, the Board of Trade and other business enterprises.

Many will wish to attend the concerts of the Symphony Orchestra or of other musical organizations which will be given during the meeting of the College; or to visit the numerous theaters. Public lectures are held weekly at the various universities. Excursions may be made around the miles of boulevard and park that surround the city, with stops at the various points of interest.

EDITORIALS

PROGRESS OR RETROGRESS

PHYSICIANS can be divided into two great groups, those that are learning and those that are forgetting, those that each year know more, and those that each year know less. There seems no third group, those that are stationary.

A few physicians increase in knowledge from within and grow from their own doing. These are the innate investigators. The rank and file require outside help to grow and to progress. Books, meetings, contacts, discussions, teachers, are our armamentarium for progress. Like the "spring tonic" of past days, all of us need some of this medicine, at least annually, better if it comes more frequently. A large majority of physicians know their need and seek treatment.

Things in nature rarely are static; they increase or they decrease; they grow or they decay; they progress or they retrogress. Man's education in many respects resembles things of nature; rarely is it static; when knowledge does not increase, almost always it decreases. Physicians should remember this and make every effort to keep out of the static state and on the side of increase, of growth, of progress.

Contact with colleagues eager to learn, listening to discussions by those capable of teaching, witnessing demonstrations and clinics, seeing scientific exhibits lead to more reading and better observation of patients. Herein lies medical progress. The meeting of the American College of Physicians provides just these opportunities. Attendance at this meeting is a potent way for a physician to get himself out of the group of those who each year know less. The stimulus received from attendance at a medical meeting where men eminent in the profession speak lasts long after the meeting is over.

HENRY A. CHRISTIAN, M.D., F.A.C.P.

THE NEW PURE FOOD AND DRUG BILL

AT THE special session of Congress last summer, Senator Copeland introduced the first draft of a bill which was designed to replace the present federal law governing the manufacture and sale of foods and drugs. The Food and Drugs Act of 1906, which was drafted by the late Dr. Harvey W. Wiley and was pushed through Congress in spite of tremendous opposition, was considered very comprehensive in scope, but time has indicated that it is not sufficiently broad in its terms to meet the needs of the present day.

The most serious omission in the Wiley act lies in its failure to give power to the Food and Drug Administration to curb the excessive and often fraudulent claims in the advertising matter issued by the less conscientious manufacturers of drugs and foods. False labeling of the con-

tainer is penalized but the far more effective propaganda of lying advertisements is beyond the reach of the law.

The use of dangerous adulterants or the addition of harmful preservatives is fairly well controlled at present, but adulteration with harmless ingredients and the sale of substandard products are difficult to control. The use of a "distinctive name" for the product permits it to escape conviction under the law.

The phraseology of the present law requires that to obtain conviction of false labeling the Food and Drug Administration must prove that the statements made are both *false* and *fraudulent*. In other words it must be shown that the manufacturer realized the falsity of his claims. The manufacturer has only to exhibit a few signed testimonials from users of his product to render plausible his statement of belief in its efficacy. It is not often that the federal authorities have as ready a rebuttal as in a recent case which was tried in Baltimore. The defendant had been selling a consumption cure consisting chiefly of turpentine and egg albumin. He based his defense largely on testimonials from patients. A federal officer was able to show, however, that of a series of testimonials from one individual, several were dated after the ascertained time of this person's death. It was eventually proved that the manufacturer had been paying for these letters and that after the death of the original author he had knowingly continued to pay the son for further testimonials to the "cure."

The present law is also defective in that it makes no provision for the supervision of the manufacture and sale of a number of chemical compounds and mechanical appliances which may seriously affect the health of those who use them. Cosmetics, for example, are not under federal supervision as to the nature of the ingredients, the conditions of manufacture or the truthfulness of the label. Medical men since 1906 have had opportunity to learn of the harm that may result from hair removers, dyes, facial creams and powders. The *Journal of the American Medical Association* has done much to keep the profession, and through them the public, informed of such dangers. Usually, however, it has been only the damage suits of the injured that have had power to force the manufacturer to discontinue the sale of his product.

Along with cosmetics, various obesity cures, radium waters, electrical belts, nose straighteners, etc., now escape legal control.

The bill introduced by Senator Copeland last summer goes a long way toward closing the loop holes which exist in the present law. According to its terms a statement of the ingredients of a compound would have to be printed not only on the label of the package, but as a part of any advertising matter. Certain incurable diseases are specified and no advertisement of a "cure" for these would be permitted. Medicines which in general medical opinion are only palliative in their effect would have to be so labeled. Cosmetics, reducing compounds and mechano-therapeutic devices would by the new act be brought under federal control. Definite standards are men-

tioned by which the purity and strength of drugs would be measured, and others to govern quality of foods. Very large powers would be granted to the Secretary of Agriculture both to promulgate regulations in the spirit of the law and to inspect and if necessary regulate the methods of manufacture. The existing penalties for misbranding, etc., would be materially increased and equally stiff penalties would follow conviction for false advertising.

The medical profession was not surprised when the introduction of the Copeland bill aroused hot opposition on the part of the manufacturers of patent medicines and of various nostrums. It was hoped that these complaints indicated that the terms of the new act would effectively hamstring some of these concerns. But when widely known and reputable drug manufacturers were found in opposition there seemed to be some cause for astonishment.

The honest objections to the bill may be briefly summarized. It is pointed out by some of its opponents that the adoption of a new act will nullify the value of the great body of favorable court decisions which have been rendered in prosecutions under the present law and that it will take years of legal battles before the new law could be as effective. Moreover, since many of the state laws are modeled after the present federal law there would be endless confusion until all state laws were revised. Such revision might in some instances be delayed through the political strength of the interests affected. The program advocated by those who are impressed by these arguments is to retain the present law but to amend it so that its more serious omissions will be adequately covered. A measure containing such amendments has already been introduced before the House of Representatives.

Many of those who concede that changed conditions have made a new bill necessary are honestly critical of certain phrases in the first draft of the Copeland bill. They feel, for example, that to declare that advertising matter may be false by "inference or ambiguity" is likely to expose even honest advertising to attack. They are not willing that decisions should be made in accord with "the general agreement of medical opinion." Probably many jurists would adhere to their point of view that such "general agreement" has proved in the past to be quite rare.

The creation of an army of inspectors to work in the manufacturer's plant is feared by many; and there is question of the right of the government to make public secret formulae and technical processes. Finally there is strong and legitimate opposition to the almost unlimited regulating powers which would be granted to the Secretary of Agriculture.

The strength of the opposition has led to the introduction in the present Congress of a revised form of the Copeland bill in which changes have been made to meet the more valid arguments against the first draft. The objectionable phases cited above have been eliminated. Secret technical processes are protected. The discretionary powers of the Secretary of State are very

much restricted. Two committees of five are to be appointed by the President, one having authority in the issuance of regulations concerning drugs and the other having similar powers as to regulations concerning foods. The Secretary of Agriculture will initiate regulations by pointing out their necessity to the committee concerned, but the form of the regulation will be determined by the majority vote of the committee whose decision will have the force of law.

The revised Copeland bill is said to be an administration measure and as such is likely to become law. It is important that sufficient time be given to its consideration by all concerned so that in its final form it may prove to be workable and effective and, at the same time, just to the public, the drug, food and cosmetic industries, and the medical profession.

The conscientious manufacturer is entitled to protection against the false advertising and substandard products of unscrupulous competitors. The physician and the pharmacist should be aided by the assurance of better standardized products. But most of all the general public should receive more protection against the advertising campaigns of patent medicine and nostrum makers who prey on the human desire for quick remedies and for cures of the incurable.

It is estimated that the sum of 360 million dollars is spent annually in this country on self medication with patent medicines other than simple home remedies. This folly, of course, will not be overcome by the passing of a new bill. Its roots lie too deep in human ignorance and superstition. Something will be accomplished, however, by stopping the encouragement of this human weakness through deceptive advertising, and by rendering the quack remedies which the public demands at least harmless in content.

The voice of the medical profession should be heard in strong support of the revised Copeland bill. The American Medical Association has for years through its Councils on Pharmacy and Chemistry, Committee on Foods and Council on Physical Therapy, advised the profession in these fields. It stands in the position of natural leadership and should place the influence of the medical profession behind the passage of a strong bill and its adequate enforcement.

REVIEWS

Malaria Treatment of Parenchymatous Syphilis of the Central Nervous System. Supplement No. 107 to Public Health Reports. By R. A. VONDERLEHR, Passed Assistant Surgeon, United States Public Health Service. Government Printing Office, Washington. 1933.

The favorable results obtained by the induction of malaria fever in the treatment of syphilis, and particularly syphilis of the central nervous system, make this paper of interest. The clinical results obtained in the treatment of parenchymatous neurosyphilis in 8,038 cases are noted by years. A summarization of these results shows that 26 per cent of the cases were able to resume their former occupation, 22.3 per cent were improved, 28.3 per cent were unimproved and 23.4 per cent had died since the induction of the malaria. The communicability of induced malaria to the general population is an important public health problem and is considered in some detail. The histologic changes in the central nervous system and various theories as to the mode of action of the plasmodial disease upon syphilis of the central nervous system are considered. The technic of malaria inoculation as well as the treatment of the induced malaria are taken up. Brief consideration is also given to the question of prognosis. Contraindications to the induction of malaria which have been noted by a number of writers are described; those most commonly mentioned are cachexia, severe organic heart disease, tuberculosis, and nephritis, and other less common contraindications are listed. Serological changes taking place in the spinal fluid are described in some detail and various administrative and sociologic problems are discussed. The complications and sequelae of malaria therapy are also described.

In addition to the treatment of parenchymatous syphilis, consideration is also given to the subject of prophylactic action of malaria in the prevention of the development of syphilis of the central nervous system and to the treatment of other forms of syphilis. A complete bibliography through the year 1931 is appended.

W. L. T.

Radiologic Maxims. By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P. 127 pages; 14 × 20 cm. Radiological Review Publishing Company, Quincy, Illinois. 1932. Price, $1.50.

The maxims in this small volume cover the broad field in which roentgenology and radium therapy are of value. They will be of interest to the internist and the surgeon. Both will note, however, a certain optimism as to the value diagnostically and therapeutically of the radiologic method. A maxim or so on the value of cooperation between the clinician and the radiologist might well have been added.

M. C. P.

New Introductory Lectures on Psychoanalysis. By SIGMUND FREUD, M.D., LL.D.; translated by W. J. H. SPROTT. 257 pages. W. W. Norton and Co., New York. 1933. Price, $3.00.

The Interpretation of Dreams. By SIGMUND FREUD, M.D., LL.D.; translated by A. A. BRILL, M.D., Columbia University. 600 pages. MacMillan Co., New York. 1933. Price, $5.00.

It is very logical that these two books should be reviewed together as they form an excellent symposium on the science and art of psychoanalysis. Both books are up-to-date revisions of Freud's work which made its first appearance in 1900 and which aroused the scientific world to a more constructive understanding of the workings of the human mind. Dr. Brill rightfully says in his introduction: "No work on psychology worthy of its name can now afford to ignore Freud's theories. . . .

They have exerted the greatest influences on the mental sciences and have practically rewritten them."

The interpretation of dreams has been a popular subject for discussion for many hundreds of years, and Freud carefully surveys the scientific literature on dreams up to 1900. He then, in a logical sequence, first discusses the method of dream interpretation—the dream as wish fulfillment, distortion in dreams, the material and sources of dreams, how the dream works, the psychology of the dream-processes, and finally ends up by giving a complete bibliography of 461 items. As Freud says: "With an appreciation of the mode of functioning of the psychic apparatus and an insight into the relation between conscious and unconscious, all that is ethically offensive in our dream-life and the life of fantasy for the most part disappears."

Freud gave his First Introductory Lectures on Psychoanalysis in 1915, and this more recent volume of lectures was prepared in the summer of 1932 in Vienna. As he states in his preface, these lectures "are addressed to that large group of educated persons to whom, let up hope, one can ascribe a benevolent, if cautious, interest in the special nature and discoveries of this young science. . . . It looks as though people did not expect from psychology progress in knowledge, but some other kind of satisfaction; every unsolved problem, every acknowledged uncertainty is turned into a ground of complaint against it." In seven chapters Freud then discusses the basic factors in the psychoanalytic process. He first takes up the interpretation of dreams, but this discussion in no way can replace the more exhaustive treatment of this subject given in his larger volume. He then discusses "the anatomy of the mental personality, anxiety and instinctual life, the psychology of woman, a philosophy of life and psychoanalytic explanations, complications and orientations."

Any person interested in a thorough study of psychoanalytic method cannot do better than to begin with the reading of these two books and continue by reading *Psychoanalysis and Medicine* by Karin Stephen, a book which was reviewed in the December issue of THE ANNALS. But the reader must remember, as Freud says in his introductory lectures: "It is exceedingly difficult to give an insight into the psychoanalysis to any one who is not himself a psychoanalyst. I assure you that we do not like to give the effect of being members of a secret society carrying on a secret science. And yet we have been obliged to recognize and state as our considered opinion that no one has a right to a say in psychoanalysis unless he has been through certain experiences which he can only have by being analyzed himself." But as Freud concludes in his *Interpretation of Dreams:* "For all practical purposes in judging human character, a man's actions and conscious expressions of thought are in most cases sufficient. Actions, above all, deserve to be placed in the front rank; for many impulses which penetrate into consciousness are neutralized by real forces in the psychic life before they find issue in action; indeed, the reason why they frequently do not encounter any psychic obstacle on their path is because the unconscious is certain of their meeting that resistance later. In any case, it is highly instructive to learn something of the intensively tilled soil from which our virtues proudly emerge. For the complexity of human character, dynamically moved in all directions, very rarely commits itself to the arbitrament of a simple alternative, as our antiquated moral philosophy would have it."

J. L. McC.

Hygiene of the Mind. By BARON ERNST VON FEUCHTERSLEBEN; translated from the German by F. C. SUMNER, Ph.D., Professor of Psychology, Howard University, Washington, D. C. 150 pages. MacMillan Company, New York. Price, $1.25.

This little book is uniquely interesting as it was written about 100 years ago by an Austrian physician, philosopher and poet, who obtained his medical degree in 1833. As Dr. Esther Loring Richards says in the introduction, the author must have been an astute observer and a reflective physician who in the course of his practice of

medicine learned to see his patients functioning as total personalities and not as physiological segments.

The author states, "I like the reader who wishes to be stimulated rather than dogmatized. The doubtful appears more interesting to me than that which has been settled. Let each one proceed with his own feet through the fields whither I point. It seems to me altogether true that all virtue is self-mastery, although not all self-mastery is virtue."

It is well for persons in this day and age, who frequently belie the fact that we are rapidly going to the dogs, to stop for a moment and read the first few lines of the introductory chapter of this very old book which states that: "Our age is fast, impetuous and frivolous. One does himself and the reading public a real mental service if one directs the gaze away from the discouraging life of a volcanic present, or from the still more discouraging vacillating literature which is falling to pieces in a thousand futile directions toward the quiet regions of the science of the inner man toward the contemplation of our Self."

He further on states: "Perhaps physicians and we ourselves have not yet devoted to this viewpoint the full attention which it deserves. For here it is a question of being one's own physician before being a physician to others." And he makes a very modern axiom of mental hygiene when he advises us "to analyze man instead of gaping at him as at a miracle."

There is no doubt that the reader could spend several stimulating hours between the covers of this book. And, although it is not written exactly in the language of our day, we come to the conclusion that the sages of the past have yet a great deal to teach us.

J. L. McC.

Diseases of Old Age. By F. MARTAN LIPSCOMB, M.R.C.P. (London), Major Royal Army Medical Corps, Deputy Surgeon of the Royal Hospital, Chelsea. vii + 472 pages; 13 × 19 cm. William Wood and Company, Baltimore. 1933. Price, $4.50.

The author has produced a very readable account of the clinical characteristics of diseases in the aged, i.e. in those above the age of 65 years. He reminds the reader quite rightly that with the decrease in infant and early adult mortality, the care of the aged is becoming an increasingly larger part of the physician's task. Many diseases are not greatly altered by the age of the patients but others show very different clinical features and still others are practically confined to the later periods of life. The book deals only with these last two categories. The clinical descriptions for the most part have the freshness derived from personal observations. The therapeutic recommendations are sane and specific. The large field covered makes brevity a requisite and at times one feels that this has resulted in inadequacy. The chapter on the nervous system is an example of excessive condensation. One might mention here that the omission of pernicious anemia as a cause of senile paraplegia is unfortunate since early detection and treatment may arrest the progress of the condition. On the other hand, this undue brevity is in part compensated for by the carefully selected references which add much to the value of the book. It is a little volume which should prove of very real value to all practitioners.

M. C. P.

COLLEGE NEWS NOTES

NOMINATIONS FOR ELECTIVE OFFICES

1934–35

The Nominating Committee herewith transmits the following nominations for elective offices of the American College of Physicians for the year 1934–1935:

President-Elect .....James Alex. Miller, New York, N. Y.
First Vice-President .....James H. Means, Boston, Mass.
Second Vice-President .....Randolph Lyons, New Orleans, La.
Third Vice-President .....James F. Churchill, San Diego, Calif.

Respectfully submitted,

per directions of the Committee,

JOHN H. MUSSER, *Chairman.*

Attest: E. R. LOVELAND.

December 27, 1933

Acknowledgment is made of the following gifts of publications to the Library by members of the College:

Dr. Franklin B. Bogart (Fellow), Chattanooga, Tenn.—five reprints;
Dr. A. Morris Ginsberg (Fellow), Kansas city, Mo.—three reprints;
Dr. Murray B. Gordon (Fellow), Brooklyn, N. Y.—six reprints;
Dr. Edward G. Huber (Fellow), Lt. Col., M. C., U. S. Army—two reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint;
Dr. Arthur H. Jackson (Associate), Washington, Conn.—one reprint;
Dr. Frederick W. Mulsow (Associate), Cedar Rapids, Ia.—two reprints.

Major John G. Knauer (Associate), Medical Corps, U. S. Army, has been transferred from Balboa Heights, Canal Zone, to Ancon, Canal Zone, where he is assistant to the Chief of the Medical Service, and Cardiologist to the Gorgas Hospital.

Dr. Howard T. Karsner, professor and director of the Institute of Pathology of the School of Medicine of Western Reserve University, Cleveland, delivered the Smith-Reed-Russell Lecture at the School of Medicine of George Washington University, Washington, D. C., on December 19. He spoke on "Rheumatic Heart Disease."

Dr. Murray B. Gordon (Fellow), Brooklyn, New York, addressed the Buffalo Academy of Medicine on "Criteria of Endocrine Disorders in Children" on November 22, 1933.

Dr. Benjamin Goldberg (Fellow), associate professor of medicine, University of Illinois College of Medicine, has been given an honorary professorship in the National University of Mexico.

Dr. James Alexander Miller (Fellow), New York City, presided at the laying of a seven ton cornerstone for the new building of the Departments of Health, Sanitation and Hospitals in New York City recently. The work was originally begun in 1931. The building will occupy an entire block, and will be ten stories high.

Dr. Henry J. John (Fellow), Cleveland, Ohio, has been appointed head of the newly created department of metabolic diseases at St. Luke's Hospital, Cleveland.

Under the auspices of the Division of University Extension of the Massachusetts State Department of Education and the Massachusetts Society for Mental Hygiene,

a course of lectures were recently given on intelligent living and on the adjustments of normal youth. Dr. Joseph H. Pratt (Fellow), Boston, gave a lecture on "The Body and the Mind" and Dr. Austen Fox Riggs (Fellow), Stockbridge, gave a lecture on "Intelligent Living."

Recently Dr. Albert H. Hoge (Fellow), Bluefield, was reappointed and Dr. Walter E. Vest (Fellow), Huntington, was newly appointed to the Public Health Council of West Virginia.

Dr. Eugene E. Murphey (Fellow), Augusta, Ga., has been elected to the Board of Trustees of the University of Georgia Hospital.

Captain Edward U. Reed, M. C., U. S. Navy (Fellow), has been ordered from command of the U. S. Navy Dispensary, San Pedro, Calif., to command the U. S. Naval Hospital, Charleston, S. C.

Dr. Franklin B. Bogart (Fellow), Chattanooga, Tenn., has been elected secretary of the Section on Radiology of the Southern Medical Association. Dr. Bogart has also been elected president of the Chattanooga and Hamilton County Medical Society for 1934.

At the last annual meeting of the American Student Health Association held in Chicago, December 27–29, 1933, Dr. R. W. Bradshaw (Associate), College Physician of Oberlin College, Oberlin, Ohio, was elected president.

Dr. Harold F. Machlan (Fellow) has been officially transferred to Washington, D. C., as Medical Supervisor, Central Office of the Veterans Administration. Dr. Machlan was formerly Clinical Director of the U. S. Veterans Administration Hospital at Dayton, Ohio.

Major Edgar Erskine Hume (Fellow), librarian of the Army Medical Library, Washington, D. C., has been awarded the Wellcome Prize for 1933, consisting of $500.00 and a gold medal, by the Association of Military Surgeons of the United States at its last annual meeting in Chicago. The prize was awarded for Major Hume's essay on "The Value of Studies in Health and Sanitation in War Planning."

After fifteen years' service as editor of the *Virginia Medical Monthly*, Dr. Alexander G. Brown, Jr. (Fellow), Richmond, Va., has resigned. For the same period of time, Dr. Brown was chairman of the Program Committee of the Medical Society of Virginia.

Dr. Francis H. Smith (Fellow), Abingdon, Va., is now president-elect of the Medical Society of Virginia.

At the last annual meeting of the Southern Medical Association, in Richmond, during November 1933, the following Fellows of the American College of Physicians were elected to the offices indicated: Dr. H. Leslie Moore, Dallas, Texas, president; Dr. Thomas A. Groover, Washington, D. C., second vice-president; Dr. Seale Harris, Birmingham, Ala., chairman of the Board of Trustees; Dr. William B. Porter, Richmond, secretary of the Section on Medicine. Dr. William deB. MacNider, professor of pharmacology at the University of North Carolina, received the annual medal for outstanding achievements in original research. Dr. Glenville Giddings received first award for scientific exhibits, and Dr. George B. Lawson, Roanoke, received honorable mention.

OBITUARIES

DR. GEORGE J. ECKEL

Dr. George J. Eckel (Fellow), Buffalo, N. Y., was born February 16, 1878, at Perrysburg, Ohio, and died October 29, 1933, in Buffalo, N. Y. He was graduated from the Perrysburg (Ohio) High School in 1898 and graduated from Canisius College with the degree of A.B. in 1903 and the degree of A.M. in 1904, and from the University of Buffalo with the degree of M.D. in 1908. He did postgraduate study in London, England, in 1916, with Dr. Thomas Lewis and in Vienna, Austria, in 1923, with Dr. Erdheim and others.

He was appointed Assistant Professor of Medicine in the University of Buffalo in 1921, Associate Professor of Medicine in 1927, and Clinical Assistant in Medicine, Buffalo General Hospital, in 1920, Consulting Internist to the U. S. Public Health Service in 1924. He was a member of the Faculty of the Medical Department of the University of Buffalo in 1910 and Attending Specialist in Internal Medicine, U. S. Marine Hospital, in 1933.

At the time of his death, he was a member of the Staff of the Buffalo General Hospital, Buffalo, Emergency Hospital, Buffalo City Hospital, Eye and Ear Dispensary and Wettlaufer Clinic, Mount Mercy Hospital and Crippled Children's Guild. He was consultant to the Staffs of the U. S. Marine Hospital and Our Lady of Victory Hospital.

Dr. George Eckel entered the U. S. Navy, April 21, 1917, as Lieutenant, Junior Grade, Medical Corps, and was discharged from the Service September 16, 1919, as Lieutenant, Senior Grade. He served at the Marine Headquarters, Buffalo, N. Y., April 21, 1917 to October 20, 1918; at receiving ship in New York City, October 24, 1918, to November 23, 1918; on board the U. S. S. S. *George Washington,* November 23, 1918, to April 10, 1919; at Marine Headquarters, Buffalo, from April 13, 1919, to September 16, 1919. He attended the Military Instruction Camp under the War Department, U. S. Army, in 1916.

The squad from the Naval Militia (New York) fired the salute over his grave and taps were sounded as a final tribute for his medical service during the World War.

He was a member of The American College of Physicians (1921), American Medical Association, Buffalo Academy of Medicine, Erie County Medical Society, New York State Medical Society, Society for the Study and Prevention of Cancer, Alumni Association of the Medical Department of the University of Buffalo, and of Omega Upsilon Phi, national fraternity.

He was a member of the War Society of Cruiser and Transport Service, Veterans of Foreign Wars, U. S. Naval Reserve, Post 368, Crew of the U. S. S. S. *George Washington,* American Red Cross, Buffalo Society of Natural Science, Erie County Society for Prevention of Cruelty to Animals,

U. S. Training Camp Association, Automobile Club of Buffalo and American Historical Society.

Dr. George Eckel had a sunny and cheery disposition, his clinical presence was pleasant and reassuring; his knowledge of medicine was deep and wide. He was an excellent diagnostician and a safe adviser. He was up-to-date in his methods. As a teacher he was well liked by his students and by other members of the teaching staff. His hospital work was good. His kindness to the ward patients was outstanding and unfailing. He had an extensive consultation practice. He was widely known among the members of the American College of Physicians and the many other medical organizations of which he was a member. His associates in medicine were always glad to see him and to return his hearty and cordial greeting. He died altogether too young, and we mourn his loss and miss him much.

ALLEN A. JONES, M.D., F.A.C.P.,
Governor for Western New York.

DR. ADRIAN HANSFORD GRIGG

Adrian Hansford Grigg, M.D. (Fellow), Beckley, W. Va., died of pneumonia after a week's illness on January 6, 1934, at the Beckley General Hospital where he had been chief of the Medical staff for over twelve years.

Dr. Grigg was born at Crown Hill, West Virginia, August 1888, and was educated in the public schools and the West Virginia University. He graduated with honors at Jefferson Medical College in 1912, being elected a member of Alpha Omega Alpha. He served his internship at the Philadelphia General Hospital. In 1913 he located in West Virginia and entered the Medical Corps of the Navy, serving at the Naval Academy during the World War with the rank of Lieutenant.

On his return he became head of the Medical Service at the Beckley General Hospital and was instrumental in its development into one of the leading hospitals in the State.

He was a member of his county and state medical societies and of the American Medical Association. In 1929 he became a Fellow of the American College of Physicians. He was also a member of Beta Theta Pi.

He left a widow and one daughter.

R. D. ROLLER, JR., M.D., F.A.C.P.,
Charleston, W. Va.